The New England
Journal of Medicine

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Volume 246 APRIL 24, 1952 Number 17

REPLACEMENT OF GASTRIC AND INTESTINAL FLUID LOSSES IN SURGERY*

A Preliminary Report

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THE proper method for the replacement of gastrointestinal fluid losses in surgery has been the subject of considerable controversy. Volume-for-volume replacement with saline solution has been advocated, but the results have not justified the procedure. The use of glucose and saline mixtures as either equivalent or less than equivalent volume replacement has been equally unsuccessful.

It is the purpose of this paper to demonstrate that volume-for-volume replacement of gastrointestinal losses does not lead to disturbances in acid-base equilibrium if replacement solutions of appropriate composition are used.

The replacement of gastrointestinal losses is only a small part of complete parenteral fluid therapy in surgical patients. Recent advances in the knowledge of water and electrolyte metabolism have complicated practical fluid therapy. For this reason a logical system of teaching and planning fluid therapy is necessary. Such a system can be deduced from simple, well known physiologic facts.

The system of planning fluid therapy that has been in use in the Department of Pediatrics of the Yale University School of Medicine for at least two years is briefly described below. It has the advantage of simplicity of terminology as well as applicability to all types and ages of patients from prematurity to senility. The three general principles of fluid therapy are: deficit therapy, maintenance therapy and concomitant replacement of abnormal losses.

The first phase is the replacement of any deficits of water and electrolyte that are present at the beginning of fluid therapy.* The amount and kind of deficit are estimated as accurately as possible from the patient's history, physical findings and laboratory data and from balance data obtained from similar patients.

The second general principle of fluid therapy is the supply of water, electrolyte, protein, calories and vitamins at a rate that approximates the rate of turnover of these materials under ordinary circumstances — so called "maintenance therapy." This turnover is a function not simply of weight or surface area but rather of total heat production — in other words, of energy expenditure. The requirements for maintenance therapy are calculated using a unit, namely, "100 calories metabolized"[1]; therefore no corrections need be made for weight, age, fever, activity, basal metabolic rate and so forth after the total energy expenditure is estimated.§

The third general principle of fluid therapy is the contemporary replacement of abnormal losses, as in burns, exudates, gastrointestinal suction, sweat and so forth. This phase of fluid therapy consists of the volume-for-volume replacement of abnormal losses by solutions approximating in composition those lost from the body either externally or into unavailable body depots. The importance of the concomitant replacement of these abnormal losses in surgery cannot be overemphasized. If parenteral fluids similar in composition to those being lost are administered at the same time and at the same rate at which abnormal losses occur, deficits in body composition are avoided; and renal adjustments, which often further increase the over-all deficits of water and electrolyte, need not occur. It is with this third general principle of fluid therapy that this paper is concerned.

The most common abnormal fluid losses in surgery occur in the gastrointestinal tract and its derivatives, the biliary tract and the pancreas. Two solutions|| have been used to replace these losses. The first solution is called "Gastric Replacement Solution" and has been used, as the name indicates, to replace the losses incurred through gastric suction or vomiting. The second solution is called "Intestinal

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This work was aided in part by a grant from the James Hudson Brown Memorial Fund.

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§The details of "maintenance therapy" will be the subject of a future communication.

||These solutions were prepared for us and Dr. Alfred Hurwitz, Newington Veterans Hospital, by Dr. Arnold E. Osterberg, Research Division, Abbott Laboratories.

Replacement Solution" and has been used to replace losses incurred through intestinal suction as well as biliary or pancreatic drainage. An approximation (derived from several sources[2-5]) of the composition of gastrointestinal secretions is represented in Figure 1, as well as the composition of the replacement solutions. The similarities are obvious.

These solutions have been administered to a number of patients. The present study consists of the review of the charts of 24 of these patients. Thirteen of these patients received replacement therapy for twenty-four to forty-eight hours only. These cases will not be reported, since no definite conclusions concerning them can be drawn because of the short duration of therapy.

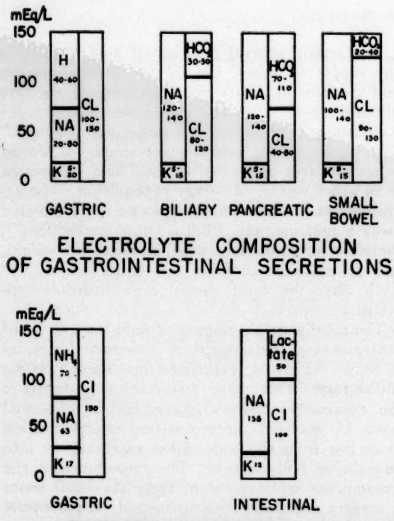

FIGURE 1. *Electrolyte Composition of Gastrointestinal Secretions and Replacement Solutions.*

TECHNIC OF ADMINISTRATION

In general these solutions were administered intravenously, through either a standard needle or a polyethylene catheter. However, they were designed to be isotonic with body fluids and occasionally were given subcutaneously without reaction. The gastric or intestinal replacement solutions were frequently mixed with other fluids used for maintenance therapy, and a 50 per cent solution of glucose was occasionally added when extra calories were indicated. At no time were they given at a rate in excess of 500 cc. per hour. The ideal procedure for determining the amount of replacement solution to be administered is as follows: A nurse carefully measures the volume of gastric or intestinal fluid obtained every four to six hours and, on instruction from the physician, adds to the infusion the equivalent volume of the appropriate solution. At the beginning of gastrointestinal suction more frequent measurements of the rate of drainage are made so that a minimal debt is incurred. In actual practice, when a shortage of nursing personnel is likely, this ideal procedure is not feasible. Under the usual circumstances a prediction is made by the physician of the volume of gastrointestinal drainage for the next twelve hours based on the volume of drainage obtained during the first few hours of suction. The correct amount of replacement solution is then added to the other fluids for the next twelve hours. At twelve-hour intervals the drainage losses and fluid intake are calculated and appropriate corrections in the rate of replacement are made. The solution to be used (gastric or intestinal replacement) is determined by the physician on the basis of the location of the drainage tube and occasionally according to the type of drainage. The color and the pH of the drainage may be deceptive, in that gastric drainage may be green and yet be of low sodium and high chloride content.

RESULTS

In all the cases studied, no evidence of toxicity could be obtained. Careful physical examination during the course of therapy revealed no evidence of central-nervous-system stimulation or depression, as might be seen from administration of an excess of ammonium ions.[6] Edema was not detected clinically in any patient. The electrocardiogram was not affected, nor were urinary abnormalities detected during or after therapy. Many of the patients were losing large amounts of water and electrolyte, up to 4500 cc. a day; none displayed *clinical* evidence of dehydration, edema or changes in acid-base equilibrium. They all expressed a feeling of well-being and many were intermittently ambulatory.

All patients received water, electrolyte, protein, calories and vitamins according to the maintenance requirements as previously described by Darrow and Pratt,[1] in addition to the replacement solutions. It is impossible to predict the course of these patients had other replacement solutions been used. However, it is fair to say that during therapy with gastric or intestinal replacement solutions there were no serious disturbances in water and electrolyte composition such as frequently occur when normal saline solution alone is employed for re-

placement. In several patients definite derangements were corrected; in all others the normal chemical structure of the extracellular fluids was maintained.

Case Reports

Case 1. A 41-year-old man had a pyloric obstruction due to ulcer, as well as high gastric acidity. Preoperatively he was placed on gastric suction for 5 days; postoperatively, for 2 days. Gastric drainage ranged from 2200 to 3600 cc. each day. Intermittent infusions were given twice a day, with volume-for-volume replacement of gastric drainage for the preceding 12 hours. The daily fluid intake was approximately 5500 cc. Clinically he appeared well, with no signs of tetany. There was no fever, leukocytosis, thrombophlebitis or cerebral symptoms. A slight elevation of the serum-bicarbonate concentration was noted during therapy, with a fall after more adequate replacement of the potassium deficit with potassium chloride. The serum-chloride concentration did not fall, despite a large volume of gastric drainage, and the nonprotein nitrogen rose somewhat but the patient was receiving large amounts of Amigen. He received a total of 12,800 cc. of gastric replacement solution in 5 days.

Table 1. *Data on Case 1.*

Date	Volume of Drainage	Volume of Gastric Replacement Solution	Serum CO_2 Content	Serum Chloride	Serum Sodium	Serum Potassium	Serum Nonprotein Nitrogen
	cc.	*cc.*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*mg./100 cc.*
6/20	2200	2000					
6/21	3600	3000	28.6	95.0	139	4.1	41
6/22	3450	2600					
6/23	3200	3700	32.3	94.2	137	3.8	59
6/24	2600	2500					
Operation							
6/25	50	0	29.4	96.0	142	4.3	60
6/26	130	0					39

Case 4. A 15-year-old girl had a right colectomy because of regional enteritis. Postoperatively she was placed on gastric suction for 5 days. Gastric drainage ranged from 175 to 275 cc. each day. Administration of gastric replacement solution was begun on the second day of suction. The sodium and chloride concentrations of the serum fell before proper therapy, with a rapid rise to normal after therapy.

Table 2. *Data on Case 4.*

Date	Volume of Drainage	Volume of Gastric Replacement Solution	Serum CO_2 Content	Serum Chloride	Serum Sodium	Serum Potassium	Serum Nonprotein Nitrogen
	cc.	*cc.*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*mg./100 cc.*
7/31	300	0					
8/1	270	250	30	84	125	3.6	
8/2	175	250	24	97	128	5.3	
8/3	175	250					
8/4	200	250	24	106	141	4.6	

Case 8. A 50-year-old man underwent gastrectomy because of bleeding ulcer. Preoperatively he was placed on gastric suction for 3 days and postoperatively for 3 days. She received a total of 1250 cc. of gastric replacement solution in 4 days.

Table 3. *Data on Case 8.*

Date	Volume of Drainage	Volume of Gastric Replacement Solution	Serum CO_2 Content	Serum Chloride	Serum Sodium	Serum Potassium	Serum Nonprotein Nitrogen
	cc.	*cc.*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*mg./100 cc.*
8/6	1150	1000					
8/7	700	500					
8/8	225	0			136		
8/9	340	250	26	94			37
8/10	275	250					
8/11	200	250	24	102	131		

Table 4. *Data on Case 10.*

Date	Volume of Drainage	Volume of Intestinal Replacement Solution	Serum CO_2 Content	Serum Chloride	Serum Sodium	Serum Potassium	Serum Nonprotein Nitrogen
	cc.	*cc.*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*mg./100 cc.*
7/23	575	1000					
7/24	350	500	28	87	127	5.2	40
7/25	450	1000					
7/26	750	1000					
7/27	100	100	27	97	135	4.4	36
7/28	100	100					

Gastric drainage ranged from 200 to 1150 cc. each day. Gastric replacement solution was administered in amounts approximately equal to the volume of gastric drainage. The serum analyses were normal at the end of therapy, by which time he was clinically well. He received a total of 2250 cc. of gastric replacement solution in 6 days.

CASE 10. A 32-year-old woman had intestinal obstruction because of a pelvic abscess. She was placed on low intestinal suction for 6 days. Drainage ranged from 100 to 750 cc. per day. Intestinal fluid replacement was carried out for 6 days with intestinal replacement solution. The patient was clinically well. There was a gradual rise in serum sodium and chloride concentration toward normal. She received a total of 3700 cc. of intestinal replacement solution in 6 days.

CASE 11. A 1½-year-old girl had appendicitis and postoperative ileus and wound dehiscence. Postoperatively she was placed on gastric suction for 2½ days and on intestinal suction for the following 4 days. Gastric drainage ranged from 100 to 280 cc. and intestinal drainage from 160 to 410 cc. per day. Gastric replacement solution was used for 1 day and intestinal replacement solution was used for 4 days. Serum analyses were limited by difficulty in obtaining blood. She was clinically well. There was no evidence of toxicity. She received a total of 125 cc. of gastric replacement solution in 1 day and a total of 1150 cc. of intestinal replacement solution in 4 days.

TABLE 5. *Data on Case 11.*

DATE	VOLUME OF GASTRIC DRAINAGE	VOLUME OF INTESTINAL DRAINAGE	VOLUME OF GASTRIC REPLACEMENT SOLUTION	VOLUME OF INTESTINAL REPLACEMENT SOLUTION	SERUM CO_2 CONTENT	SERUM CHLORIDE	SERUM SODIUM	SERUM POTASSIUM	SERUM NONPROTEIN NITROGEN
	cc.	*cc.*	*cc.*	*cc.*	*milliequiv. / liter*	*milliequiv. / liter*	*milliequiv. liter*	*milliequiv. / liter*	*mg. /100 cc.*
7/9	100								
7/10	280		125						
7/11	?		0						
7/12	25	125		250	21	92	125	4.2	20
7/13		410		425					
7/14		225		225					
7/15		160		250					

DISCUSSION

It is impossible to duplicate exactly the composition of gastric, intestinal, pancreatic or biliary drainage in each patient. Not only is there a wide range among different patients,[3] but also drainage differs somewhat in composition in the same patient from day to day. Gastric replacement solution was prepared in order to supply approximately half the chloride in combination with ammonium ions. Since the ammonium is readily metabolized, chloride is left in the extracellular space in excess of sodium. This excess of chloride over sodium is characteristic of most gastric secretion except in severe achlorhydria. The actual ratio of chloride to sodium ions in this solution is somewhat lower than in some gastric analyses. However, a higher concentration of ammonium ion might induce a severe metabolic acidosis in an occasional patient. The concentration of potassium (17 milliequiv. per liter) in the gastric replacement solution is a high average

TABLE 6.

CASE NO.	PATIENT	AGE	DISEASE	REGION OF SUCTION	DAYS OF SUCTION	AVERAGE SUCTION PER DAY	TYPE OF REPLACEMENT SOLUTION	AVERAGE AMOUNT OF REPLACEMENT SOLUTION	REMARKS
						cc.		*cc.*	
1	A	41	Pyloric obstruction due to ulcer	Stomach	6	3000	Gastric*	3000	Slight rise in nonprotein nitrogen. Also received large doses of Amigen. Condition excellent.
2	C	48	Perforated ulcer	Gastric	4	1000	Gastric	600	Serum analyses rose to normal after proper gastric replacement for 3 days
3	H	2	Intussusception	Stomach	3	150	Gastric	200	Normal serum analyses
4	K	15	Right colectomy for regional ileitis	Stomach	5	225	Gastric	250	Serum chemical rose to normal after gastric replacement
5	B	76	Pyloric obstruction, duodenal perforation, gastroenterostomy	Stomach	11	2500	Gastric	1500	Proper gastric replacement began late; chloride elevated to normal by treatment.
6	M	45	Perforated duodenal ulcer	Stomach	8	2500	Gastric	1700	Serum analyses remained normal throughout
7	P	32	Perforated ulcer with infectious hepatitis	Stomach	4	1500	Gastric	1200	Increasing amounts of gastric replacement led to normal serum analyses
8	T	50	Gastrectomy for bleeding ulcer	Stomach	6	400	Gastric	300	Essentially normal serum analyses throughout
9	P	65	Cancer of bladder with perforation into ileum, ileostomy	Ileostomy	12	500	Intestinal†	500	Normal serum analyses throughout
10	M	32	Pelvic abscess with intestinal obstruction	Jejunum	6	500	Intestinal	600	Serum analyses became normal at end of treatment
11	T	1½	Postoperative ileus after appendectomy	Stomach and ileum	4	300	Intestinal	300	Sodium and chloride fell slightly

*The solution of ammonium, potassium and sodium-chloride (Abbott).
†The solution of sodium chloride, sodium lactate and potassium chloride (Abbott).

of our analyses and those in the literature.[2-4] It seems unlikely that this concentration of potassium could produce toxic plasma levels in the presence of adequate urine formation.

Gastric replacement solution was designed as an isotonic solution, even though the material obtained by gastric suction may be hypotonic in many cases.[3] Its isotonicity permits its use by hypodermoclysis. Furthermore, in the individual patient it is impossible to determine routinely the composition of gastric suction except in research laboratories. Therefore a solution that supplies to the occasional patient a slight excess of electrolyte was considered more advisable than one that might not supply enough. This assumption seems justified by a study of our cases, in which there seemed to be a greater tendency to falling or low serum sodium and chloride concentrations, without expanded extracellular volumes, than to high or rising concentrations.

Gastric replacement solution provides chloride in excess of sodium and thereby prevents the development of metabolic extracellular alkalosis. It is this alkalosis that leads to severe intracellular potassium depletion.[7]

Intestinal replacement solution provides sodium in excess of chloride and thereby prevents the development of metabolic acidosis, such as was formerly seen in pancreatic or biliary fistulas or in low gastrointestinal obstruction, ileostomies and diarrhea. The concentrations of sodium and chloride are approximately those of extracellular fluid. The potassium concentration of the replacement solution (12 milliequiv. per liter) is about the mean of our analyses of pancreatic, biliary and lower-intestinal secretions.

In hospitals without facilities for the determination of serum sodium and potassium, these solutions may safely be used to replace abnormal losses from the gastrointestinal tract. Other fluids must also be administered for maintenance therapy. These replacement solutions do *not* supply adequate amounts of water, sodium, potassium, chloride, protein or calories for the complete therapy of the patient. The serum carbon-dioxide content or combining power should be determined at approximately two-day intervals during therapy. If the serum-bicarbonate concentration falls unduly while gastric replacement solution is being used to replace gastric drainage, intestinal replacement solution may be substituted for it, since under those circumstances sodium would probably be removed in excess of chloride in the gastric drainage. Because of the rapid conversion of ammonium ions to urea, ammonium-ion poisoning cannot occur if the solutions are administered at a rate that approximates that of gastric drainage. As much as 15 cc. of gastric replacement solution per kg. of body weight per hour may be given without danger of accumulation of ammonium ions.[6]

Perhaps the most important advantage of these solutions lies in the fact that they are ready-made solutions that can be easily administered directly from the container by the nurses and are suitable for the replacement of all gastrointestinal losses. It is true that more accurately determined replacement solutions for an individual case can be concocted by a surgeon familiar with metabolic problems through the use of varying mixtures of glucose, normal saline, potassium chloride, sodium lactate or bicarbonate or ammonium chloride, as recommended by specialists in the field. However, the preparation of these home-made mixtures is time-consuming, wasteful and expensive. On most hospital services such mixtures will not be made, and saline solution alone will probably be administered by a busy house staff as replacement therapy.

Summary

A system of concomitant replacement of abnormal losses from the gastrointestinal tract in surgical patients is described. A gastric replacement solution that provides an excess of chloride over sodium ions as well as some potassium is advised. An intestinal replacement solution that provides an excess of sodium over chloride ions as well as some potassium is suggested.

References

1. Darrow, D. C., and Pratt, E. L. Fluid therapy: relation to tissue composition and expenditure of water and electrolyte. *J. A. M. A.* **143:** 365-373 and 432-439, 1950.
2. Gamble, J. L. *Companionship of Water and Electrolytes in the Organization of Body Fluids.* Lane Medical Lectures. Vol. 5. No. 1. Stanford, California: Stanford University Press, 1951.
3. Lockwood, J. S., and Randall, H. T. Place of electrolyte studies in surgical patients. *Bull. New York Acad. Med.* **25**:228-243, 1949.
4. Darrow, D. C. Body fluid physiology: relation of tissue composition to problems of water and electrolyte balance. *New Eng. J. Med.* **233**:91-97, 1945.
5. Unpublished data of the authors.
6. Bodansky, O. Recent advances in parenteral fluid therapy with ammonium chloride and potassium. *Am. J. M. Sc.* **218**:567-586, 1949.
7. Darrow, D. C., Schwartz, R., Iannucci, J. F., and Coville, F. Relation of serum bicarbonate concentration to muscle composition. *J. Clin. Investigation* **27**:198-208, 1948.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA*

A Clinicopathological Correlation

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THE most accurate method of study of any disease is enlightened statistical analysis of a large number of cases. However, paroxysmal nocturnal hemoglobinuria is a rare blood dyscrasia; approximately 45 cases, not all of convincing authenticity, have appeared in the literature to this time.[9] Consequently, no physician or group of physicians is likely to collect a number sufficient to be of statistical significance. Therefore, in this disease an older method, that of long-term observation of a few cases, must be relied on to add to the common stock of medical knowledge. This paper is based on clinical observation of two classical cases over a five-year period and on pathological examination of one.

Paroxysmal nocturnal hemoglobinuria is an uncommon hemolytic disease which occurs principally in young persons. The laboratory findings of accelerated blood destruction are present. The anemia is usually quite intense and is accompanied by reticulocytosis, icterus and leukopenia. The characteristic feature is hemoglobinuria occurring after sleep and demonstrated in the morning urines. Splenomegaly and lymphadenopathy are commonly present. Although supportive measures may maintain the life of the patient, the disease progresses relentlessly and has never been known to disappear either spontaneously or therapeutically.

Although the basic physiologic abnormality was first noted by the Dutch physician van den Bergh,[10] the present-day worker Ham is foremost among the students of this disease.[11-14] Ham's work, confirmed by Dacie,[9-15] demonstrated that the hemolysis was related to the physiologic drop in the pH of the serum occurring during sleep. This was supported by the experimental demonstration that if a suspension of the patient's red blood cells was added to slightly acidified autogenous or heterogenous serum, even if the pH was within physiologic limits, marked hemolysis resulted. This hemolysis would not occur with normal cells similarly suspended in acidified saline solution. It does occur, however, in the presence of the patient's own serum or normal serum from other persons. During sleep the pH normally drops slightly, and it is during this period that hemolysis occurs. Should the patient sleep during the day and be awake during the night the hemoglobinuria is diurnal. The administration of acid salts, such as ammonium chloride, provokes a hemolytic crisis.

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CASE REPORTS

CASE 1. B. B., a 29-year-old man, was well until 3 years before admission to the Cedars of Lebanon Hospital, at which time he suffered an episode of renal colic, terminating in the passage of a small stone. He felt ill and was noted to be pale after this but suffered no definite symptoms until 3 months before admission. After a heavy alcoholic debauch, followed by eighteen holes of golf, he passed smoky urine. This did not recur, and no attention was given it. About 10 days before admission he developed upper-abdominal distress that led to his hospitalization. Examination of the blood on admission revealed 2,100,000 erythrocytes and 3200 leukocytes per cu. mm., of which 30 per cent were polymorphonuclear cells. The hemoglobin was 40 per cent, the icteric index 20 units and the reticulocyte count 7 per cent. The spleen was moderately enlarged and there was slight generalized lymphadenopathy. During the entire hospitalization period of 10 weeks no hemoglobinuria was apparent although it was repeatedly searched for. The patient's hemoglobin gradually fell to 27 per cent. Several transfusions brought this up to 67 per cent. The icteric index decreased and the previous slight fever disappeared. The patient was subsequently followed in the outpatient department.

As a diagnostic test, 4 gm. of ammonium chloride was given daily for 3 days. This provoked a minor hemolytic crisis. The Ham acid-hemolysis test *in vitro* was positive at this time. Finally, approximately 6 months after his discharge from the hospital, the patient began to show, on occasional mornings, slight hemoglobinuria. In retrospect, it is probable that the disease had already been present 4 years before the appearance of the nocturnal hemoglobinuria.

During the remaining 4 years of his life he received multiple transfusions, which maintained him in a fair degree of health. One month before his death he developed fever and a pain in the left tonsillar fossa, associated with severe hemoglobinuria and a precipitous drop in hemoglobin. There was an irregular ulcer with a necrotic base in the tonsillar fossa that simulated those seen in agranulocytic angina. At that time the white-cell count was 2000, with 22 per cent polymorphonuclear cells. The infection responded to penicillin, but no sooner had the fever disappeared than the patient suffered a severe colicky pain in the right flank associated with hematuria. Cystoscopy revealed bleeding from the right ureteral orifice. At this time the bleeding and clotting times were normal, and the platelet count was 170,000 per cu. mm. On the fourth day the patient abruptly went into shock and died.

Autopsy (Da-26-46) performed 1 hour and 40 minutes after death, revealed a normal heart. The left and right lungs weighed 330 and 390 gm. respectively. Numerous focal areas of hemorrhage were observed grossly. Microscopically an occasional small blood vessel showing thrombosis was also seen.

The spleen was slightly enlarged, weighing 220 gm. The parenchyma was dark red and the splenic follicles were prominent. Microscopically, these follicles showed small secondary nodules. Focal hemorrhage could be seen in the capsule. There was no hemosiderosis.

Both the mediastinal and abdominal lymph nodes were moderately enlarged and somewhat fleshy in appearance. Microscopically, a pronounced reticuloendothelial hyperplasia could be seen. Some of these cells were vacuolated. No hemosiderin deposits were observed.

The stomach was moderately distended. Two large acute ulcers, 3 and 10 cm. in diameter, were observed along the lesser curvature. In the areas of the ulcers the stomach wall revealed extensive hemorrhagic discoloration extending throughout the entire thickness of the wall. Microscopically, the blood vessels in the region of the ulcers revealed evidence

of recent thrombosis. The stomach wall in the areas presented extensive hemorrhagic necrosis, suggestive of infarction, with regional leukocytic infiltration.

The small intestine contained a moderate amount of hemorrhagic fluid. There were six segmental areas of hemorrhagic infarction of the jejunum and ileum, varying in width from several cm. to approximately 10 cm. in width. Microscopically, the regional blood vessels revealed recent thrombosis with varying degrees of organization of the blood clot. Three distinct processes seemed to be involved. In some of the blood vessels the erythrocytes appeared to be clumped, suggesting intravascular agglutination. In other places the red cells were indistinct, suggestive of lysis. These two possibilities were also indicated by the fact that in the region of uninvolved blood vessels the erythrocytes could be seen as distinct and well preserved structures. The third process involved in the thrombosis seemed to be the formation of fibrin clots primarily consisting of relatively few cells and abundant fibrin. These observations excluded consideration of the older thrombi, in which cytologic detail was also lost.

The liver weighed 1990 gm. and was softer than normal. Repeated section revealed a distinct loss in the architectural details. The lobules were poorly defined; there were moderate cloudy swelling and fatty change; many of the small and moderate sized intrinsic veins revealed thrombi. Microscopically, the thrombi showed varying degrees of organization. In addition, there was extensive focal hemorrhagic necrosis of the tissue, representing areas of infarction.

The left kidney weighed 140 gm., the right 180 gm. In the perinephric fat on the right side there was extensive hemorrhage, which surrounded the kidney and dissected into the peripelvic fat and along the right ureter into the retroperitoneal pelvic tissues. No hemorrhage was observed on the left side. Both kidneys were unusually brown. On section the cortex was distinctly brown; the normal striations were obscured. The pyramids of the right kidney were slightly obscured, but those of the left were not remarkable. The right ureter was patent to a probe in its entirety, but the wall was markedly thickened and showed extensive hemorrhagic discoloration. The left ureter was normal in appearance.

Microscopical examination of sections of the kidneys revealed a marked deposition of hemosiderin in the cells of the convoluted tubules, which explains the brown discoloration of the cortex. The glomeruli were univolved. The pyramids presented no histologic abnormality. The peripelvic veins, in the areas of hemorrhage, showed evidence of thrombosis. Two of the regional arteries also presented unusual calcification of the media. Considerable reactive polymorphonuclear leukocytic infiltration was found. Sections of the ureter showed extensive hemorrhage of the entire thickness of the wall, with considerable reactive leukocytic infiltration. An occasional vein showed evidence of thrombosis.

The bladder was small, containing only a small amount of hemorrhagic fluid. The wall was markedly thickened by hemorrhage; leukocytic infiltration and thrombosis of intrinsic veins could be seen.

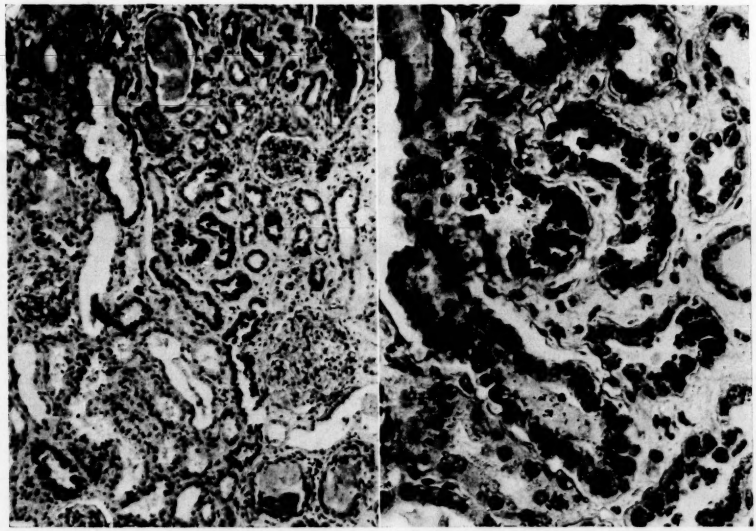

FIGURE 1. *Low- and High-Power Magnification of Sections of Renal Parenchyma from Case 1. The renal tubules show a heavy deposit of hemosiderin in the epithelial cells. Some of the tubules are diseased, showing distention of the lumen, flattening of the epithelium and hyaline plugs.*

CASE 2. R. P., a 41-year-old woman, was well until 11 years before her admission to the Cedars of Lebanon Hospital, at which time she noted weakness and slight fever. Three months later nocturnal hemoglobinuria appeared. Her history for the next 5 years was one of continual bouts of nocturnal hemoglobinuria and progressive anemia. Three years before admission a splenectomy was performed; this did not alter the picture of the disease. Examination of the blood on admission revealed the following: red blood cells, 1,860,000; hemoglobin, 38 per cent; white blood cells, 6800; platelets, 260,000; icteric index, 40 per cent; reticulocyte count, 12 per cent.

The urine was shown to contain oxyhemoglobin on both chemical and spectroscopic examination. She had been subject to vague but severe upper-abdominal and lumbar pain in association with active hemolysis. However, she suffered an attack of unusually intense upper-abdominal pain during hospitalization that was associated with vomiting and relieved by nitroglycerin. It was noted that her icterus deepened markedly after this attack and that bile appeared in the urine. At surgery a gall bladder containing many small stones was removed, and the common duct was cleared of several concretions; subsequently the icterus decreased moderately and the bile disappeared from the urine. A Ham acid-hemolysis test was positive on several occasions.

During the 5 years following her discharge she has consistently shown an elevated icteric index and reticulocyte count, as well as a progressive anemia that has necessitated many transfusions.

Discussion

The title "paroxysmal nocturnal hemoglobinuria," like so many other descriptive names of diseases, is a misnomer. In the first place, unless the patient suffers from nocturia, the hemoglobinuria occurs in the morning on arising and is not nocturnal. Secondly, the title unfortunately stresses the hemoglobinuric aspect of the disease, which is inconstant, and suggests that the diagnosis cannot be made in its absence. Although it had been considered, the disease was not recognized during the initial phase of the illness in Case 1 because of the absence of hemoglobinuria in the presence of progressive anemia. In both cases there were occasional long periods of no hemoglobinuria, although at the same time the blood counts continued to fall and the patients were icteric. The anhemoglobinuric phase of this disease has not been sufficiently stressed in the literature. Ottenberg[16] has demonstrated a renal threshold for hemoglobin, the level being about 30 mg. per cent. As long as the hemolysis is not sufficiently rapid to produce a hemoglobin serum level greater than the threshold, no hemoglobinuria will result. Therefore, the patients may remain anhemoglobinuric in spite of active hemolysis.

Although no cases of this syndrome without hemoglobinuria have been reported, it is probable that such mild cases do exist and are regarded as atypical hemolytic anemia. Patients with atypical hemolytic anemia, even without hemoglobinuria, should be subject to the acid-hemolysis test to rule out this possibility.

It must be emphasized that, although the hemoglobinuria may be absent over long periods of time, the hemolysis continues and the disease is not arrested. The patient is naturally elated to arise in the morning and pass clear yellow urine, seizing on the hope that his disease is arrested. Nevertheless, even during these anhemoglobinuric episodes, both the patients herein reported demonstrated an elevated icterus, an abnormally high reticulocyte count and a decreasing red-cell count.

In both cases the hemoglobinuria could be initiated at will by factors other than sleep. In the second case the patient stated that two drugs could cause her hemoglobinuria, riboflavin and aspirin. Three mg. of riboflavin by hypodermic injection twice daily distinctly provoked hemoglobinuria, as did 4 gm. of aspirin by mouth. Both these drugs were subsequently given to the first patient. The aspirin provoked hemoglobinuria; the riboflavin had no effect. Large doses of aspirin used in the treatment of rheumatic fever have been shown to produce acidosis, and it was probably through this mechanism that hemoglobinuria was induced. The quantity of riboflavin was too small to affect the pH of the blood, and the hemolytic reaction in the second case suggests a hypersensitivity to the drug.

When any intercurrent infection developed, an identical pattern of response followed in both cases. During the febrile period the urine showed hemoglobin during all or most of the day even though the patient was awake. The hemoglobin level dropped alarmingly during this period, occasionally falling 20 points. On the day the patient became afebrile the urine would clear completely and remain clear for as long as two weeks, during which time the hemoglobin might rise slightly. However, the patient was never able to raise the level of hemoglobin significantly without aid, and transfusions were needed after every significant febrile bout. Consequently influenza, sore throats or even severe colds caused considerable concern to both patient and physician. On several occasions the hemolytic crisis provoked by the fever was sufficient actually to threaten life, and on almost every occasion transfusions were necessary.

The effect of transfusions was spectacular in each case. Unfortunately, at times both patients were likely to get severe febrile transfusion reactions not due to blood incompatibility; when this occurred the hemolysis and hemoglobinuria were so intense that the final hemoglobin level of the blood was occasionally less than the initial hemoglobin level. When the transfusion was given without incident the signs of hemolysis were less pronounced, and the urine frequently cleared completely. The higher the hemoglobin was elevated, the longer the absence of hemoglobinuria. On one occasion in the first case, when the hemoglobin was elevated to 67 per cent there was no hemoglobinuria for two months. It was readily apparent that in these patients transfusions had more than a replacement value; they clearly slowed or occasionally suspended the hemolytic process temporarily. Fewer transfusions were necessary to maintain the patient at a hemoglobin of 70 per cent than at 40 per cent.

Transfusions are especially effective because red cells are administered; these cannot be hemolyzed by the disease. The patient can only hemolyze his own abnormal red cells, since the hemolytic process is ineffective against normal cells. The situation here parallels the administration of RH negative blood to a child with erythroblastosis fetalis and differs from the usual state in hemolytic anemia

in which the administration of blood is dangerous because of the patient's tendency to hemolyze the transfused red cells.

Although leukopenia is regarded by most observers as a constant feature of the disease, it was present in the first but not in the second case. The second patient had previously had a splenectomy, which may account for the normal white-cell count. Splenic hypertrophy by itself is able to produce leukopenia, as exemplified in thrombosis of the splenic vein, Banti's disease and cirrhosis; in these diseases splenectomy usually restores the white-cell count to normal. It is likely that a parallel situation exists in paroxysmal nocturnal hemoglobinuria.

That the leukopenia may approach alarming levels is demonstrated by the first case. The white-cell count fell to 2000, with only 22 per cent granulocytes. During this period the patient developed the clinical picture of granulopenic angina, with a necrotic lesion of the pharynx.

Attention must be called to the abdominal pains suffered by both these patients. In the first case a paroxysm of hemoglobinuria would be associated with upper-abdominal distress and a sense of tightness in the back. On one occasion the pain was referred to the left upper quadrant and was so severe that opiates were required. A diagnosis of infarction of the spleen was made, but the autopsy, about one month later, showed no evidence of infarction. The second patient was subject to severe back pains in association with hemolytic crises. Since similar pains are known to occur in unrelated hemolytic anemias, such as sickle-cell anemia and Lederer's acute hemolytic anemia, it is probable that they did not reflect an intrinsic feature of paroxysmal nocturnal hemoglobinuria but are secondary in a nonspecific manner to the hemolysis.

The nature of the final episode in the first case is difficult to explain. Apparently the actual cause was massive hemorrhage into the urinary tract, but why this should occur in the presence of an adequate platelet count (170,000 per cu. mm.) and a normal bleeding and clotting time is not apparent. Vascular thrombosis, however, is frequently seen in pathological study of paroxysmal nocturnal hemoglobinuria.[17]

The pathology of this disease is somewhat variable. The striking finding in our case was multiple thromboses in the gastrointestinal tract, with ulceration, and in the genitourinary tract with hemorrhage so severe as to be the actual cause of death. The thrombosis appears to be the primary disturbance rather than the ulceration or the hemorrhage. Such thromboses occur in other hemolytic diseases, such as sickle-cell anemia and acute hemolytic anemia. There is no evident explanation for these multiple thromboses.

A second pathological finding in paroxysmal nocturnal hemoglobinuria is the remarkable distribution of the iron pigment. In most hemolytic diseases hemosiderin is deposited generally through the reticuloendothelial system and is evident in the spleen, liver and lymph nodes. Our patient showed no hemosiderosis of these areas; hemosiderin was found only in the renal tubules, a striking finding in view of the long duration of the disease and the large number of transfusions. This suggests that the actual breakdown of the red cell occurs in the epithelium of the renal tubules.

During this five-year period of observation, both patients were subjected to various types of experimental therapy. Hoffman[18] had reported that pilocarpine caused the hemoglobinuria to disappear. This drug was entirely without value in either of these cases. Sodium citrate in the test tube inhibits the hemolytic reaction; it had no significant effect on either patient.

Vitamin C is reputed to be capable of combining with oxygen and increasing the oxygen-carrying capacity of the serum; administration of 500 mg. a day caused only a slight increase in these patients' hemolysis. Tetrathione, said to increase the oxygen content of arterial blood, also brought about only a slight increase in the hemolytic rate in one patient. Administration of the amphoteric alkalis, such as Amphogel, did not effect the hemolysis. The soluble alkalinizing agents were considered too dangerous to use. Injections of crude and refined liver were similarly without benefit.

Summary and Conclusions

Two cases of paroxysmal nocturnal hemoglobinuria have been observed over a four-year period. The basic feature of this disease is hemolysis and subsequent hemoglobinuria occurring during sleep, which has been shown to be a result of the physiologic drop in pH of the blood at that time. The disease may have long anhemoglobinuric phases, early in its course in particular, and therefore will be recognized only when all cases of atypical hemolytic anemia are routinely subjected to the acid-hemolysis test. During these anhemoglobinuric phases the actual hemolysis continues, but at a slower rate. Any fever precipitates a hemolytic crisis and may be a threat to the life of the patient.

The leukopenia seen in the first case was sufficiently severe to simulate agranulocytic angina; it was not present in the second patient, whose spleen had been removed. It was therefore probably due to the nonspecific splenomegaly. Transfusions not only acted as replacement therapy but actually slowed the hemolytic process. No other method of treatment demonstrated any value.

Autopsy in one case revealed massive hemorrhage into the genitourinary tract that was the cause of death. There were multiple thromboses of the gastrointestinal tract and the kidney. These thromboses are probably the cause of the intra-abdominal pain that is a common feature in paroxysmal nocturnal

hemoglobinuria. Another unusual autopsy finding was the confinement of hemosiderin deposits to the renal tubules and its absence from the reticuloendothelial system of the liver and abdominal nodes.

References

1. Witts, L. J. Paroxysmal haemoglobinurias. *Lancet* **2**:115-120, 1936.
2. Hegglin, R. Die chronische hämolytische Anämie mit nächtlicher Hämoglobinurie (Typus Marchiafava). *Helvet. med. acta* **10**:27-29, 1943.
3. Dacie, J. V., and Gilpin, A. Refractory anemia (Fanconi type): its incidence in three members of one family, with in one case a relationship to chronic haemolytic anaemia with nocturnal haemoglobinuria (Marchiafava-Micheli disease or "nocturnal haemoglobinuria"). *Arch. Dis. Child.* **19**:155-162, 1944.
4. Milne, J. A. Case of nocturnal haemoglobinuria. *Brit. M. J.* **2**:84, 1945.
5. Buell, A., and Mettier, S. R. Paroxysmal nocturnal hemoglobinuria with hemolytic anemia (Marchiafava-Micheli syndrome). *J. Lab. & Clin. Med.* **26**:1434-1439, 1941.
6. Flynn, J. E. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria. *J. Iowa M. Soc.* **35**:255-259, 1945.
7. Dacie, J. V., and Firth, D. Blood transfusion in nocturnal haemoglobinuria. *Brit. M. J.* **1**:626-628, 1943.
8. Pierce, P. P., and Aldrich, C. A. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome): report of case with marked thrombocytopenia in 5-year-old child. *J. Pediat.* **22**:30-42, 1943.
9. Hamburger, L. P., and Bernstein, A. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria. *Am. J. M. Sc.* **192**:301-316, 1936.
10. van den Bergh, A. A. Ictère hémolytique avec crises hémoglobiniques: fragilité globulaire. *Rev. de méd.* **31**:63-69, 1911.
11. Ham, T. H., and Dingle, J. H. Studies on destruction of red blood cells: chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria: certain immunological aspects of hemolytic mechanism with special reference to serum complement. *J. Clin. Investigation* **18**:657-672, 1939.
12. Ham, T. H. Studies on destruction of red blood cells: chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria: investigation of mechanism of hemolysis, with observations on 5 cases. *Arch. Int. Med.* **64**:1271-1305, 1939.
13. Ham, G. C., and Horack, H. M. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinemia: report of case with only occasional hemoglobinuria and with complete autopsy. *Arch. Int. Med.* **67**:735-745, 1941.
14. Ham, T. H. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria: study of mechanism of hemolysis in relation to acid-base equilibrium. *New Eng. J. Med.* **217**:915-917, 1937.
15. Dacie, J. V., Israels, M. C. G., and Wilkinson, J. F. Paroxysmal nocturnal haemoglobinuria of Marchiafava type. *Lancet* **1**:479-482, 1938.
16. Ottenberg, R., and Fox, C. L., Jr. Rate of removal of hemoglobin from circulation and its renal threshold in human beings. *Am. J. Physiol.* **123**:516-525, 1938.
17. Scott, R. B., Robb-Smith, A. H. T., and Scowen, E. F. Marchiafava-Micheli syndrome of nocturnal haemoglobinuria with haemolytic anemia. *Quart. J. Med.* **7**:95-114, 1938.
18. Hoffman, B. J., and Kracke, R. R. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria: case report with experimental studies. *J. Lab. & Clin. Med.* **28**:817-828, 1943.

HYPERTENSIVE TOXEMIAS OF PREGNANCY*

A Simplified Method of Management Using a Purified Extract of *Veratrum Viride*

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VERATRUM viride has been used for many years in the treatment of toxemia of pregnancy,[1] and several recent reports have attested to its value.[2, 3] However, the effectiveness of the drug has been hampered by the use of crude extracts that were variable in composition and effect, making dosage adjustment difficult and toxic reactions frequent. Since purified extracts of Veratrum have been developed for the treatment of essential hypertension,[4, 5] it seemed pertinent to investigate the effects of such extracts in the toxemias of pregnancy. The availability of purified, well assayed extracts of uniform potency has permitted standard dosage and dosage schedules, thus greatly simplifying the use of the drug.

Aqueous injectable Vergitryl‡ (a purified extract of *Veratrum viride* containing known concentrations of the hypotensive ester alkaloids — germitrine, neogermitrine and germidine), was used as the principal therapeutic agent in 122 cases of hypertensive toxemias of pregnancy. This report describes standardized methods of dosage administration and an analysis of the results obtained.

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This investigation was supported by research grants from the National Heart Institute, the National Institute of Health and the Squibb Institute for Medical Research, New Brunswick, New Jersey.

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‡Vergitryl was supplied by Dr. H. Sidney Newcomer of the Medical Division of E. R. Squibb & Sons, New York.

Methods of Administration and Dosage

At the beginning of the investigation a variety of individual dosages and dosage schedules were evaluated. These preliminary studies are not included in this report.

The finding that the average effective intramuscular dose was 0.75 unit (0.5 cc.) permitted the adoption of the following schedule for nonconvulsive toxemias of pregnancy, including post-partum preeclampsia:

Give Vergitryl, 0.75 unit (0.5 cc.) mixed with 1 cc. of 1 per cent procaine solution intramuscularly at once.

Record blood pressure and pulse every half hour.

Repeat Vergitryl, 0.75 unit intramuscularly, whenever the blood pressure is over 140/90. Vergitryl may be given as often as every hour, if necessary.

If there is no hypotensive effect from 0.75 unit of Vergitryl at the end of one hour, increase dosage to 0.9 unit (0.6 cc.).

If nausea or vomiting occurs, give 50 mg. pentobarbital sodium intravenously.

Observations of the blood-pressure chart and evaluation of the patient will soon inform the physician of the patient's sensitivity to Veratrum. Indeed, it may be said that the patient will put herself on her own dosage schedule. For example,

one may find that 0.75 unit of Vergitryl will maintain the blood pressure under 140/90 for three hours or for six hours. Vergitryl is then repeated at three-hour or six-hour intervals as the case demands. The amount and the dosage interval vary from patient to patient without correlation with the initial height of the blood pressure or the severity of the toxemic state. The management of each patient, therefore, must be individualized.

Since the patient with a convulsive toxemia of pregnancy is a medical emergency, the intravenous route for administering Vergitryl is utilized.

Mix 1.5 units (1 cc.) of Vergitryl with 20 cc. of 5 per cent dextrose in water for intravenous use.

With one physician recording the blood pressure every minute and another administering the medication, give the Vergitryl solution intravenously at a rate of 1 cc. per minute until the first 20-mm. fall in systolic or 10-mm. reduction in diastolic pressure occurs.

Leave the needle in the vein. Do not give additional Vergitryl, for there will frequently be a precipitous drop in pressure in the subsequent one to two minutes.

If after one to two minutes no such reduction occurs, proceed with Vergitryl administration at a rate of 1 cc. per minute, stopping at the first subsequent sign of hypotension.

Remove the needle. Replace the needle with a 15-gauge needle through which a sterile polyethylene plastic catheter is threaded well into the vein.

Remove the 15-gauge needle and tape the catheter to the skin of the forearm.

Begin giving a solution of 5 per cent dextrose in water through the catheter to ensure patency. All additional medications are given through this catheter.

After the first hypotensive effect of Vergitryl has been witnessed, the catheter being in place, blood-pressure recordings are made at fifteen-minute intervals. Additional Vergitryl (half the previous effective dose) is given whenever the blood pressure is 140/90 or above. Once again, a few hours of observation of the blood-pressure chart and clinical appraisal of the patient will demonstrate the need for Vergitryl at definite intervals, such as every forty minutes or every two hours, the interval between injections becoming longer as the severity of the condition diminishes. If vomiting occurs, 50 mg. of pentobarbital sodium is administered intravenously.

The decision concerning the time and type of delivery is left entirely to the obstetrician. After the blood pressure has been stabilized for twenty-four to forty-eight hours, if a viable fetus is present, the easiest method of delivery is resorted to. During labor and delivery, if the patient is allowed to deliver from below, and similarly during surgery, if cesarean section is selected as the method of delivery, there is no change in the Vergitryl regimen. The same routine is followed during the first twenty-four hours or until the blood pressure has become stable and signs and symptoms of toxemia have disappeared.

Results

Duration of Action and Correlation of Dosage to the Hypotensive Response

Intramuscularly given Vergitryl begins to show its hypotensive effect in thirty minutes and reaches its peak of action in forty-five minutes. The duration of hypotension is variable, lasting from one hour to eight hours; the average is three-and-one-half to four hours.

An effective intravenous dose of Vergitryl in the mixture used (1.5 units in 20 cc. of 5 per cent dextrose in water) has its hypotensive action in one to two minutes. The duration of action is again variable, depending on the individual sensitivity to the drug, the amount of anxiety and tension present and the severity of the toxemic state.

Veratrum is an "all-or-none" drug. For example, if 0.75 unit is the effective intramuscular dose in an individual patient, 0.5 unit or 0.65 unit will have no hypotensive effect.

Toxicity and Safety of Vergitryl

Intramuscularly given Vergitryl caused pain at the site of injection. This local reaction was greatly minimized by mixing 1 cc. of 1 per cent procaine solution in the same syringe with the Vergitryl. The only systemic toxic manifestations of Vergitryl were related to the gastrointestinal tract and were probably due to the vagal stimulation produced by the drug. Increased salivation, nausea, vomiting and diarrhea were seen. The increased salivation frequently precedes vomiting. When seen alone, it was transitory and was seldom objectionable.

Table 1. *Incidence of Vomiting in All Cases Treated with Vergitryl.*

Type of Toxemia	Total No. of Cases	Cases Exhibiting Vomiting
Eclampsia	8	7
Moderate to severe pre-eclampsia	17	4
Mild pre-eclampsia	36	3
Hypertension (essential) plus superimposed toxemia	15	3
Post-partum toxemia	46	4
Totals	122	21

Nausea and vomiting were seen in 21 of the 122 cases (16 per cent). These toxic manifestations were most common after intravenous administration of Vergitryl, occurring in 7 out of 8 cases (Table 1).

After intravenous administration of Vergitryl the vomiting may precede the hypotension by a few

minutes, but it was frequently associated with the fall in pressure and lasted for five to ten minutes. Successive doses produced less vomiting. Vomiting, though alarming if not expected, was never so severe as to require parenterally given fluids.

Excluding those cases treated by the intravenous route, vomiting was seen in only 11 per cent of cases. When vomiting resulted from intramuscular administration of Vergitryl it occurred fifteen to twenty minutes after injection, thus preceding the peak hypotensive effect by one-half hour. Unlike the intravenous administration, no increased incidence of vomiting occurred when the dosage was increased from 0.75 unit to 0.9 unit or 1.05 units.

Of the many drugs used to combat vomiting, including methantheline bromide (Banthine), dibenhydrinate (Dramamine) and atropine, small intravenous doses of a barbiturate were found to be most effective. In this series 50 mg. of pentobarbital sodium was given whenever vomiting occurred. Furthermore, since vomiting is more frequent if the stomach is full an attempt was made to regulate the schedule so that Vergitryl was not given less than one hour before or two hours after a meal. Mild diarrhea occurred in only 3 of the 122 cases (2 per cent) and did not require special treatment.

Tolerance was not observed after intramuscular medication. However, there were 2 instances of tachyphylaxis after Vergitryl had been administered intravenously. This phenomenon was characterized by a temporary complete insensitivity to the drug. This occurred after a relatively large amount of Veratrum had been given and lasted three to four hours. When medication was withheld during this period, the patient again responded to the usual doses of the drug.

To our knowledge, no deaths due to Veratrum have been reported in the literature. Two errors in dosage serve to prove the wide margin of safety of Vergitryl. An eighteen-year-old Negress with moderately severe pre-eclampsia was erroneously given 0.75 unit of Vergitryl undiluted, intravenously. Almost immediately she began to vomit profusely and developed vasomotor collapse, the blood pressure being 40/20 and the pulse 45 beats per minute. Four doses of 1 mg. each of atropine sulfate, given intravenously at five-minute intervals, resulted in cessation of the vomiting and return of the blood pressure and pulse to normal limits within a thirty-minute period. Four hours later the patient delivered a normal infant. No further toxic manifestations were seen.

A seventy-six-year-old Negress with hypertensive encephalopathy was being treated on the Medical Service with Vergitryl given intramuscularly in doses of 0.75 unit every six hours. A dose of 3.75 units of Vergitryl was given by mistake instead of the prescribed 0.75 unit. In fifteen minutes the patient was found in a state of marked collapse, the blood pressure being unobtainable. Atropine sulfate in large intravenous doses was ineffective. However, intravenous administration of Neosynephrine and ephedrine restored the arterial pressure to 140/75. Four hours later the patient was conscious and the subsequent course was uneventful.

Analysis of Case Results

Eclampsia. Eight patients with convulsive toxemias were studied. In one of these, eclampsia occurred in the post-partum period. In the early part of the study, 2 patients were treated with intramuscularly given Vergitryl exclusively. Despite a good over-all result (control of blood pressure, cessation of convulsions and survival of both the mothers and the babies), the necessity for frequent injection and the delayed action of the drug when given by this route made it seem more desirable to treat the remaining convulsive toxemia cases with intravenously given Vergitryl.

An excellent result (4 cases) is defined as prompt control of convulsions, decreasing symptoms of toxemia, minimal nausea and vomiting and a living fetus. A good result (2 cases) is defined as prompt control of convulsions, decreasing symptoms of toxemia, moderate nausea and vomiting and a living fetus. A fair result (2 cases) is defined as prompt control of convulsions, decreasing symptoms of toxemia, moderate vomiting and death of the fetus.

The following case illustrates the necessity of careful observation and prompt and intensive treatment with Vergitryl in eclampsia patients.

Case Reports

Case 1. E. G., a 24-year-old Negress (primigravida), was admitted in the 34th week of pregnancy with a history of dizziness, frontal headache and edema of the ankles of two weeks' duration, all symptoms having gradually increased in severity. She had two generalized convulsions on the day of admission. She had had no prenatal care. She was in a convulsion when seen in the admitting office. The blood pressure was 210/110. Funduscopic examination revealed arteriolar spasm with a retinal sheen. There was edema of the face, hands and pretibial region. The heart and lungs were within normal limits. Abdominal examination revealed a thirty-four-week intrauterine pregnancy. Examination of the urine revealed++++ albuminuria.

A polyethylene catheter was inserted into the brachial vein and infusion of a solution of 5 per cent dextrose in water was started. Vergitryl (1.5 units in 20 cc. of 5 per cent dextrose in water) was given intravenously, and a total dose of 0.3 unit produced a fall in blood pressure from 210/105 to 150/95. The effect of this initial dose on the blood pressure lasted 45 minutes (Fig. 1). During preparation of the perineum, the blood pressure was inadvertently allowed to rise to 175/105 and then to 240/90, at which time a convulsion occurred. Vergitryl was immediately administered in a dose of 0.375 unit; this produced a prompt fall in pressure to 110/80. The blood pressure remained under 150/100 for 3 hours, during which time one additional intravenous injection of 0.3 unit Vergitryl was given. For a period of 25 minutes the blood pressure was not recorded. There was a sudden elevation to 170/105, which was not treated promptly. Further elevation to 225/110 followed, and the patient had her second convulsion while under therapy. Vergitryl, 0.3 unit, again caused a prompt reduction in pressure to 120/75. From this point on, blood pressures were recorded promptly at 15-minute intervals, Vergitryl being administered through

the polyethylene tubing whenever there was a rise to 140/90. For the remaining 27 hours the patient remained fully conscious, the average blood pressure for this period being approximately 150/100. A total dose of 4.1 units of Vergitryl was given in the 28-hour period. Twenty-four hours after admission, a low-flap cesarean section was performed under ether and gas anesthesia; a living infant was delivered. After the operation the blood pressure was recorded at 15-minute

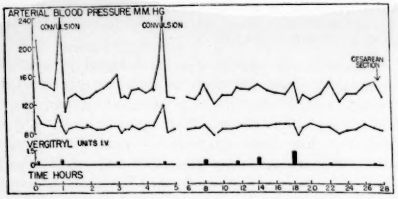

FIGURE 1. *Chart of Arterial Blood Pressure of Patient E. G.*

intervals for 8 hours, Vergitryl being given intravenously for 8 hours intravenously whenever the blood pressure rose over 140/90. Only two 0.3-unit injections were needed. The remainder of the course was uneventful.

Comment. The direct relation between the elevation of blood pressure and the production of convulsions is clearly seen. Furthermore, since the patient was fully conscious throughout her toxemic period, she was able to inform the staff of periods of anxiety and increased tension. This subjective tension was soon followed by a rise in arterial pressure and then by a convulsion. For this reason it seemed evident that increased anxiety was the first indication of the need for further treatment. Vergitryl not only lowered the blood pressure but also relieved the feeling of anxiety.

The urinary output was excellent — more than 2000 cc. the first 24 hours and more than 3500 cc. daily from then on. Edema was lessened 8 hours after admission, and examination of the retina 6 hours after admission showed a marked reduction in arteriolar spasm. Vomiting occurred on two occasions and was readily controlled by 50 mg. of pentobarbital sodium given intravenously. Finally, the use of the polyethylene catheter not only permitted repeated painless administration of intravenous medication but also did away with the need of restraining the patient.

Moderate to severe pre-eclampsia. Patients with blood pressures over 150/100, facial and ankle edema and albuminuria, — particularly if they were below the age of twenty, — were diagnosed as having severe pre-eclampsia. If one of these three findings was absent, they were then classified as moderate pre-eclampsia. There were 9 cases of severe pre-eclampsia and 8 cases of moderately severe pre-eclampsia.

The results in the 17 cases of moderate to severe pre-eclampsia are listed in Table 2. An excellent result (11 cases) is defined as a good hypotensive response, disappearance of symptoms, decrease of edema and no toxicity. A good result (6 cases) is defined as a satisfactory hypotensive response, disappearance of symptoms and decrease of edema, with mild nausea and vomiting. A fair response

TABLE 2. *Summary of Results of Treatment With Vergitryl of Nonconvulsive Toxemias.*

TYPE OF TOXEMIA	NO. OF CASES	RESULTS			
		EXCELLENT	GOOD	FAIR	POOR
Moderate to severe pre-eclampsia	17	11	6		
Mild pre-eclampsia	36	30	6		
Hypertension plus superimposed toxemia	15	10	3	1	1
Post-partum toxemias	46	41	3	2	
Totals	114	92	18	3	1

consists in a moderate hypotensive response and decreasing symptoms and signs of toxemia, with moderate vomiting. A poor response is defined as no hypotensive response or the presence of a hypotensive response with severe vomiting.

CASE 2. G. S., a 15-year-old primigravida, was admitted in the 7th month of pregnancy with a history of an uneventful prenatal course until 1 week before entry, when she noted the development of massive swelling of the ankles and face and moderate occipital headache. Physical examination revealed a blood pressure of 170/130. There was spasm of the retinal arteries. The heart and lungs were normal. Abdominal examination revealed a 7-month intrauterine pregnancy. There was massive edema of the face, hands and feet. Urin-

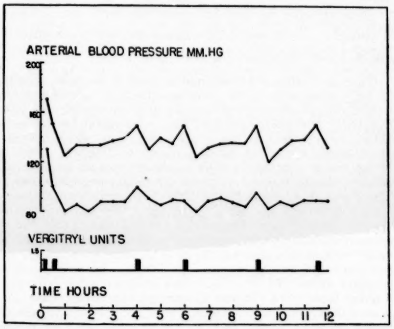

FIGURE 2. *Chart of Arterial Blood Pressure of Patient G. S.*

alysis revealed +++ albuminuria. The patient received 14 intramuscular injections of 0.75 unit of Vergitryl during the 4-day period prior to delivery (Fig. 2). On the 4th day the fetal membranes were ruptured and she delivered a normal living infant. During the 4-day period following delivery she received 15 0.75-unit intramuscular doses of Vergitryl, and the blood pressure remained under 140/90.

Comment. The patient was fully conscious at all times and was able to eat a salt-free diet. No vomiting occurred. The urinary output remained excellent and edema decreased twenty-four hours after the institution of Vergitryl. The absence of tolerance following intramuscular Vergitryl has permitted the control of the toxemic state for as long as ten days in 3 patients studied.

Mild pre-eclampsia. Patients with blood pressures over 140/90 with or without albuminuria and with or without edema, who had no hypertensive vascular changes in the retinas were diagnosed as mild pre-eclampsia.

The results in the 36 cases of mild pre-eclampsia are listed in Table 2. There were 30 excellent results and 6 good results.

CASE 3. A. C., a 22-year-old primigravida, was admitted at term in early labor, having had no prenatal care. There had been no signs or symptoms of toxemia, except for a 39-pound weight gain. Examination on admission showed a blood pressure of 160/100 and the presence of + edema of the ankles. Urine examination was negative for albumin. An intramuscular injection of Vergitryl (0.75 unit) resulted in a fall in blood pressure to 140/85, where it remained for five hours. After an uneventful delivery, the blood pressure gradually rose to 160/100, necessitating a second Vergitryl injection, which caused a prompt reduction in blood pressure to 120/80. In 3 hours the blood pressure rose to 150/100. After a third and final intramuscular injection of Vergitryl, no further treatment was necessary.

Hypertension (essential) with superimposed toxemia. Patients who were admitted with a history of hypertension antedating their pregnancy and who showed an elevated arterial pressure, hypertensive retinal changes and peripheral edema without congestive heart failure were diagnosed as having essential hypertension with superimposed toxemia.

The results in the 15 cases studied are listed in Table 2. There were 10 excellent results, 3 good results, 1 fair result and 1 poor result.

CASE 4. L. T., a 41-year-old multigravida, was admitted in early labor with profuse vaginal bleeding. Her history revealed the presence of asymptomatic hypertension of 4 years' duration. Her pregnancy had been uneventful until 2 weeks before entry, when edema of the ankles was noted. Physical examination showed a blood pressure of 210/150, Grade II hypertensive vascular changes in the retina and + peripheral edema. There was no evidence of congestive heart failure. There was + albuminuria. A 0.75-unit intramuscular dose of Vergitryl caused the blood pressure to fall to 95/55. During the next 8 hours there was a gradual rise to 160/110. A second injection caused the blood pressure to drop to 130/80, and it remained under 140/90 for 4 hours. Five 0.75-unit injections in all were given prior to delivery, keeping the blood pressure under 140/90. There was an uneventful delivery of a living infant. In the first 24 post-partum hours, two intramuscular injections of Vergitryl were needed to maintain the blood pressure under 140/90. From then on, no specific hypotensive therapy was given. The blood pressure gradually rose to 180/120, where it stabilized. The patient left the hospital without permission on the 5th post-partum day.

Post-partum pre-eclampsia. Patients who had a normal pregnancy with no signs or symptoms of toxemia but after delivery had an elevated blood pressure above 140/90 were diagnosed as post-partum pre-eclampsia.

The results in the 46 cases of post-partum pre-eclampsia are listed in Table 2. There were 41 excellent results, 3 good results and 2 fair results.

CASE 5. G. B., a 34-year-old multigravida, was admitted in early labor. Her pregnancy had been uneventful. The blood pressure on admission was 140/85. There was no edema and no albuminuria. Fifteen minutes after a normal spontaneous delivery, the blood pressure was 180/100. Vergitryl, 0.75 unit, was given intramuscularly, with a resultant fall in blood pressure to 135/80. The blood pressure did not rise for 2 hours, after which it was recorded as 160/100. A second Vergitryl injection was then given, and the blood pressure fell to 120/60 in ½ hour. There was no further elevation of arterial pressure above 140/90.

Comment. A sudden rise in arterial pressure is commonly seen in the immediate post-partum period and is occasionally the forerunner of an unexpected convulsion. The intramuscular use of Vergitryl has been particularly gratifying in this group of patients, since frequently one injection is all that is necessary for control of the blood pressure.

DISCUSSION

In spite of extensive clinical and pharmacologic investigation, the exact mode of action of Veratrum remains undetermined.[6] Studies, however, have revealed that there is stimulation of the afferent vagus-nerve endings in the heart and carotid sinus.[7, 8] From the brain, impulses travel out on unknown pathways, causing vasodilatation. They also pass down the vagus (efferent) to the heart, producing bradycardia.[7] It was because of this bradycardia that the drug was formerly thought to be a myocardial depressant.

The hemodynamic aspects of Veratrum have been thoroughly studied by Freis, and his coworkers, who clearly demonstrated that Veratrum lowers blood pressure without decreasing cardiac output, that the bradycardia is blocked by atropine whereas the hypotension may be overcome by ephedrine, that there is only a transient decrease in renal blood flow and glomerular filtration and that Veratrum does not interfere with sympathetic reflexes.[9] In short, after an effective dose the circulation is left unchanged except that the arterial pressure is lower.

Through the past fifty years *Veratrum viride* has been continually and successfully used in the treatment of pre-eclampsia and eclampsia at the Cincinnati General Hospital.[3] In 196 successive cases of eclampsia treated in the past nineteen years, there was only 1 maternal death resulting from eclampsia *per se* — a mortality rate of 0.5 per cent. This enviable record certainly speaks for itself. Why, then, has Veratrum not been more widely used in the management of toxemias of pregnancy?

The main objection to the use of Veratrum has been the effect on the urinary output.[10-12] Recent studies have shown that although a transitory decrease in the hourly urine volume is observed in some patients, this decrease being more marked when there is profound hypotension due to large

doses of the drug, the oliguria is succeeded by a marked polyuria.[9, 13] Moreover, Vergitryl administered as described herein seldom produces a drastic fall in blood pressure to shock levels, and the transitory decrease in urinary output is scarcely noticeable. Since Veratrum has been proved an effective, safe agent in the treatment of toxemias of pregnancy and since its effect on urinary output has been clarified, the refusal to accept the drug may well have been due to difficulties in the method of administration caused by the lack of a well standardized product.

The management of a patient in convulsion is an emergency necessitating prompt reduction of arterial pressure; hence intravenous administration of Vergitryl is resorted to. Fortunately, however, eclampsia is a comparatively rare disease, even in city-hospital wards. In the past ten years at Gallinger Municipal Hospital, which has a large number of patients who have had no prenatal care, there have been only 5 to 8 cases of eclampsia a year. On the other hand, nonconvulsive hypertensive toxemias have been extremely common. The availability of Vergitryl and its effectiveness by the intramuscular route in standard dosage have greatly simplified the management of such nonconvulsive cases, permitting the patient to be followed safely by the resident and nursing staff.

The control of hypertension, with concomitant alleviation of the toxemia symptoms without the use of large doses of sedatives, is a great advantage. It not only allows the patient to take nourishment by mouth, thus better preparing her for delivery or surgery or both, but also permits her to keep the physician informed of any untoward symptoms. Furthermore, hypertensive toxemias are frequently seen in the seventh or eighth month of pregnancy, which are crucial months in the development of the fetus. The large doses of sedatives routinely employed in the management of toxemias certainly have a deleterious effect on the premature infant. In our 75 cases of ante-partum toxemias, there have been only 2 fetal deaths. The fetal heart was not heard for two days prior to the institution of Vergitryl in one of these cases. The single fetal death following institution of therapy was seen in a convulsive toxemia.

Summary

A simplified and safe method of management of the hypertensive toxemias of pregnancy using a purified extract of Veratrum is outlined.

In 8 cases of convulsive toxemias, intravenous administration of Vergitryl gave excellent results in 4, good results in 2 and fair results in 2.

In 114 cases of nonconvulsive toxemias of pregnancy, intramuscular administration of Vergitryl provided excellent results in 92, good results in 18, fair results in 3 and a poor result in only 1.

There were no maternal deaths and only 2 fetal deaths.

Vomiting has been the only toxic manifestation. It occurred in 16 per cent of the cases and was readily controlled with moderate doses of pentobarbital sodium administered intravenously.

The uniform response to Vergitryl permits standardization of dosage. However, the principles of dosage discussed herein must be rigidly followed.

The author is indebted to Drs. Andrew Marchetti and John Parks, whose guidance and constructive criticism stimulated this study, and to the resident and nursing staff for their co-operation.

References

1. Bryant, R. D., and Fleming, J. G. Veratrum viride in treatment of eclampsia. *J. A. M. A.* **115**:1333-1339, 1940.
2. Assali, N. S. Studies on veratrum viride: standardization of intravenous technique and its clinical application in treatment of toxemia of pregnancy. *Am. J. Obst. & Gynec.* **60**:387-394, 1950.
3. Garber, S. T., Assali, N. S., Kistner, R. W., and Prystowsky, H. Studies related to treatment of toxemia of pregnancy. *Am. J. Obst. & Gynec.* **60**:315-323, 1950.
4. Freis, E. D., Finnerty, F. A., Jr., and Walsh, W. B. Treatment of severe essential hypertension. *M. Clin. North America* **34**:1741-1750, 1950.
5. Freis, E. D., and Stanton, J. R. Clinical evaluation of veratrum viride in treatment of essential hypertension. *Am. Heart J.* **36**: 723-738, 1948.
6. Krayer, O., and Acheson, G. H. Pharmacology of veratrum alkaloids. *Physiol. Rev.* **36**:383-446, 1946.
7. Krayer, O., Wood, E. H., and Montes, D. G. Studies on veratrum alkaloids: sites of heart rate lowering action of veratridine. *J. Pharmacol. & Exper. Therap.* **79**:215-224, 1943.
8. Moe, G. K., Bassett, D. L., and Krayer, O. Studies on veratrum alkaloids: effect of veratridine and cevine upon circulation in anesthetized dogs, with particular reference to femoral arterial flow. *J. Pharmacol. & Exper. Therap.* **80**:272-284, 1944.
9. Freis, E. D., et al. Hemodynamic effects of hypotensive drugs in man: veratrum viride. *J. Clin. Investigation* **28**:353-368, 1949.
10. Willson, J. R. Action of Veratrone on blood pressure, urine volume and urea clearance in toxemias of pregnancy. *Am. J. Obst. & Gynec.* **49**:665-672, 1945.
11. *Idem.* Veratrum viride in treatment of toxemias of pregnancy. *J. Obst. & Gynec.* **52**:273-283, 1946.
12. *Idem.* Observations on use of veratrum viride in toxemias of pregnancy. *M. Clin. North America* **32**:1673-1682, 1948.
13. Assali, N. S., Kistner, R. W., and Garber, S. T. Effect of veratrum viride on urine volume, blood pressure and pulse rate in normal and toxemic pregnancy. *Am. J. Obst. & Gynec.* **58**:90-100, 1949.

MEDICAL PROGRESS

RADIATION THERAPY OF CARCINOMA OF THE CERVIX

A Review of Fundamental Considerations

JOHN D. REEVES, M.D.*

BOSTON

THROUGHOUT most of the medical world radiation therapy is the treatment of choice in carcinoma of the cervix.[1-15] In a few centers the surgical approach is being re-evaluated with a view to ascertaining whether modern technics have reduced the excessive morbidity and mortality that prohibited the use of surgery in the past. Although the results of surgery in early cases have compared favorably with those of radiation, these results were obtained in highly selected cases, and no comparable series of radiation-treated patients exists. There is every reason to expect that if a comparable series were studied, the results of radiation therapy would prove at least equal to those of surgery.

A comparison of the best available figures shows that the five-year survival rate with radiation is equal to or better than that with surgery in all stages of carcinoma of the cervix. In addition, the physical, psychologic and economic trauma of radiotherapy may well be less than that of surgery. To quote Cade and Lederman[4]:

> The Wertheim operation is characterized by a degree of mutilation which is proportional to the radical extent of the operation. This operation, if properly performed, virtually entails the removal of most of the female genital tract. It requires little imagination to picture the probable consequences of an operation of this nature on the patient's psychological make-up and marital life. By contrast the patient successfully treated by radiotherapy is left with an atrophic, nonfunctioning, but anatomically intact genital tract. Nevertheless, whilst the case for radiotherapy as the method of choice in the treatment of carcinoma of the cervix remains indisputable, it is important not to lose sight of the fact that with a disease such as cancer for which there is no certain method of cure, it is easy to be biased in favor of one or other method of treatment. If a patient is to receive the best treatment it is equally important for her to avoid falling into the hands of a radium enthusiast as into those of a surgical enthusiast. Each employs the method he knows best, and this may not coincide with the best interests of the patient. To safeguard the patient against the risk of misguided enthusiasm she should be seen by both surgeon and radiotherapist in consultation together, and treatment decided only after such consultation.

Regardless of personal feeling about the efficacy of surgery or radiation, it should be realized that as things now stand the great majority of patients with cervical cancer will sooner or later require radiation therapy. A report published in 1949 by Heyman, Donaldson and Scheffey[4, 16] concerning 32,293 patients in twenty-four centers in eight countries reveals that 91 per cent (30,299) of the patients received radiotherapy. Although this percentage may not be quite as great at the present time, published statistics indicate that even in those centers where surgery is the primary treatment of choice the majority of patients receive radiation either primarily or secondarily.

It seems important, therefore, for any physician who may deal with patients having cervical carcinoma to acquire a certain familiarity with some of the basic fundamentals of proper radiotherapy. These notes are intended not for the expert in the field but rather for the nonradiologist who may wish to extend his knowledge of things radiologic.

PALLIATIVE OR CURATIVE THERAPY?

The distinction between "palliative" and "curative" radiation therapy is frequently not clear in the minds of those not intimately acquainted with the field of radiology. Many hasty conclusions have been drawn concerning the inability of radiation to "cure" by those who failed to realize that only palliation was intended. "Palliation" means to ease the patient's symptoms without attempting to "cure" the disease, to improve his general condition and make his disease more tolerable. Radiation therapy often relieves pain produced by both inflammatory and malignant disease. Palliative radiation therapy may temporarily discourage the growth of a tumor, — indeed, may actually cause remissions for extended periods of time, — stop hemorrhage, cause cessation of discharge and cause "lumps" to disappear and ulcers to heal. The object of palliation is to prolong life and make the patient's remaining days more comfortable.

In the palliation of cancer, radiotherapy holds an undisputed and perhaps unenvied position of distinction. Later discussion deals primarily with "curative" therapy.

RADIOSENSITIVITY VERSUS RADIOCURABILITY

Radiosensitivity and radiocurability are not synonymous terms. For example, lymphomas are very radiosensitive, whereas osteogenic sarcomas are very radioresistant — yet the absolute radiocurability of the two groups is similar.[17] (This illustrative parallel should not be construed to derogate the importance of radiation therapy in the proper management of lymphomas.) In a general

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way, radiosensitivity applies to a gross clinical impression, whereas radiocurability is applicable for the most part to a more precise microscopical or biochemical impression, which may be available before a clinical impression can be gained.

The estimation and determination of radiocurability is one of the most fascinating and critically important researches now being carried out in many laboratories. The work of Glücksmann and his coworkers,[17-21] pertaining to the cell count of tissue sections and evaluation of the response on the proximal and distal tumor bed, offers considerable promise if it can be successfully carried on by others. Likewise, the vaginal-smear methods of Graham and others[22, 23] and the demonstration of the uptake of radioactive phosphorus by cervical cancer by Sturgis and his co-workers[24] may prove most valuable.

Lymph Nodes

It has long been possible in many cases to control squamous-cell carcinoma metastatic in the lymph nodes of the neck by the proper use of interstitial radium and x-ray therapy. For this and other reasons, many radiotherapists have contended that metastatic carcinoma in the pelvic lymph nodes could also be controlled *if* the proper dose were delivered to them. With present-day technical advances, as well as improved applications of older technics, it has been shown that adequate doses can be delivered to the pelvic nodes. Further, direct and indirect evidence now indicates that metastatic intrapelvic disease may be clinically controlled if not obliterated by radiotherapy.[1, 25-30]

A knowledge of the pathogenesis and lymphatic drainage of carcinoma of the cervix is as important to proper radiation therapy as it is to proper surgery. Henriksen[29, 30] has undertaken an exhaustive study of lymphatic spread of carcinoma of the cervix; anyone treating this disease should be familiar with his work.

The more or less routine use of carbon-dioxide pneumoperitoneum to demonstrate pelvic tumors and enlarged nodes deserves consideration as another diagnostic adjunct in the evaluation of cervical carcinoma, since its advocates state that the procedure is no more formidable than the intravenous pyelogram and may be carried out at the same time.[31]

When it is discovered at the time of surgery that a tumor is inoperable and that lymph-node metastases are present and unresectable, it is of considerable help in the planning and execution of subsequent radiation therapy if the tumor and nodes are suitably marked by metallic clips or sutures.

The Fallacy of "Milligram Hours"

The unit of x-ray dose, the *roentgen*, was first defined in 1928. By 1937, after many painstaking research efforts, physicists were able to define the roentgens delivered by radium under specific conditions.[4] The accepted definition today is as follows: "The roentgen shall be that amount of x or gamma radiation such that the associated corpuscular emission per 0.001293 gram of air produces, in air, ions carrying 1 electrostatic unit of quantity of electricity of either sign." (0.001293 gm. is the mass of 1 cc. of air under standard conditions.)

Despite the fact that this basis for measuring radium therapy has been available for over fifteen years, outside the field of radiology "milligram hours" is still frequently accepted as the measurement of radium dosage. Holmes and Schulz have said:

> Unless this is qualified by a statement of the *distance factors*, the *filtration*, the *arrangement of sources*, and the *volume of tissue irradiated*, the term is quite meaningless for clinical therapy. The same is true for such terms as millicurie hours or millicuries destroyed. It is about as meaningful as the expression of dosage of roentgen rays in terms of milliampere seconds. The only logical way of expressing radium dosage is the same way as for x-ray dosage; that is, in terms of the amount of ionization it produces. This is expressed in terms of roentgen and for radium is called the gamma roentgen (rγ). The gamma roentgen has been quite accurately measured: 1 mgm. radium in equilibrium at a point source filtered with 0.5 mm. platinum being now accepted as giving 8.4 r per hour at 1 cm. distance.

Treatment of carcinoma of the cervix with radium and with the measurement of radium dosage expressed in terms of milligram hours, although it may have been successful in the hands of a few whom long years of experience have made adept, is an empiric method without scientific basis of expression and is incapable of being communicated accurately to others.

Figures 1 and 2 illustrate the fallibility of the method. It assumes that the same-sized tumor with a 1.5-cm. radius occurs in each of three different-sized uteri and that it is located, conveniently, opposite the midpoint of each of three radium applicators. The length of the applicator depends on the length of the uterine canal. The amount of radium actually used is unimportant for this discussion; the dose in each case shall be 3000 "milligram hours." If a dose of 6000 gamma roentgens is considered adequate, it will be noted that in the case of the large uterus the dose delivered to the periphery of the tumor will be inadequate; in the medium-sized uterus, adequate; and in the small uterus, more than adequate. An interesting observation is the variation of dosage opposite the ends of the applicators.

With an increased number of radium sources and a more irregular distribution of tumor, the dosage variation may be much greater. The time factor must also be considered. Without calculation of dosage in *roentgens* it is not possible to decide with any accuracy whether the lesion may have been undertreated or is "radioresistant." (Many so-called radioresistant tumors may be only improperly treated tumors.) Nor can it be stated what areas may have been overtreated. To undertreat one

small area of tumor may result in failure as surely as would inadequate surgical removal; to overtreat may result in necrosis or other dire sequelae. If dosage calculations have been incomplete or inaccurate one must avoid the temptation to blame radium for apparent failures or unwanted results.

In addition to making certain that vulnerable tissues (such as those of rectum and bladder) do not receive excessive doses, it is necessary to have some means of evaluating and comparing the dosage received by the cervix. For this purpose, the so-called Point A and Point B (as proposed by the

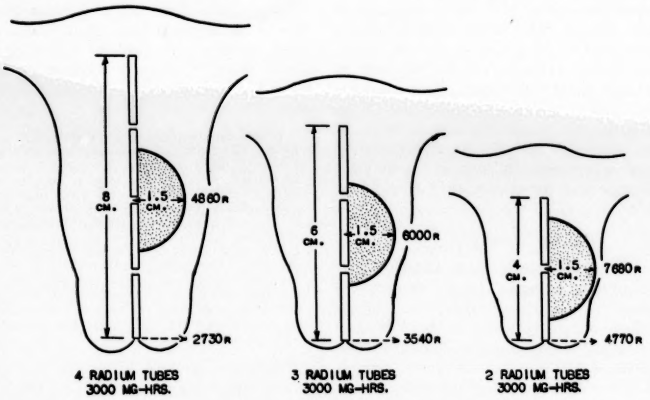

FIGURE 1. *Variations of Dosage With Variations in Geometry.*

That would be as sensible as to blame the scalpel for poor results of improper surgery.

TISSUE DOSAGE

The art of delivering a cancerocidal dose throughout the potentially tumor-bearing area without causing irreversible damage to the normal tissues requires not only a knowledge of anatomy and pathology but a well founded understanding of radiation physics and radiobiology. Although individual variation must always be considered, the following generalities regarding dosage are used as a base line.

Manchester group — Figure 3) have been widely accepted. Point A is defined as being a point 2 cm. above the mucosa of the lateral vaginal fornix and 2 cm. lateral to the uterine canal; Point B is at the same level but 5 cm. lateral to the uterine canal. The dosage at Point A gives an idea of that received in the cervix and its immediate neighborhood (the "paracervical triangle"); an isodose ellipse from Point A may pass the crossing of the ureter and uterine artery, although this anatomical landmark varies in position and can be as far lateral as 3.5 cm. from the internal os.[32] The dose at Point B, relative to that at Point A, gives an estimation of the "la-

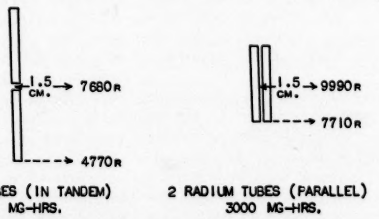

FIGURE 2. *The Same Amount of Radium Applied for the Same Length of Time But With Different Distribution Results in Different Doses at the Same Point.*
The dose opposite the ends of the parallel sources exceeds that opposite the center of the tandem sources.

teral throw" of radiation as well as an indication of what the pelvic lymph nodes may receive. Other points of pertinent dosage have received different designations by different authors; the dose should

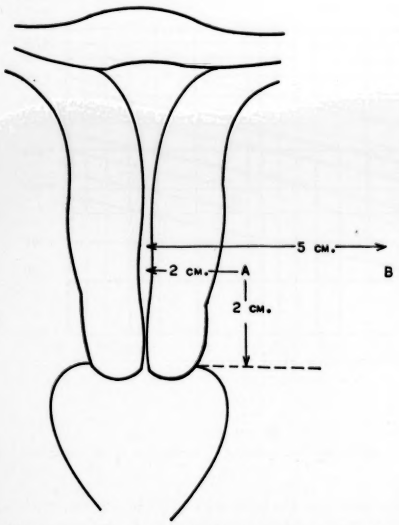

FIGURE 3. *Point A and Point B as Defined by the Manchester Group.*

be determined at the periphery of the tumor and in the lymph-node areas as well as in vulnerable normal tissues.

To control squamous-cell carcinoma, Paterson, Tod and others[4, 10, 11, 33-38] have suggested the following: Doses below 5000 r in two weeks are relatively ineffectual; by the time the dose has reached 6000 r the possibility of cure is increasing; 7000 r is a more ideal dose; and when 8000 r is given, the cure rate is approaching its maximum (Fig. 4). Thus it is good judgment to deliver the higher dose if the tumor is of a size and in a position to allow it and if the age and condition of the patient will permit. However, the maximum tolerable dose is not always the ideal dose. If the dose exceeds the limits of tissue tolerance, not only will damage occur to normal tissues but the control of the cancer itself will not be so effective. This is the "supralethal effect," which is probably due to an adverse effect on the tumor bed.

The uterine musculature may withstand doses of 15,000 to 30,000 r. Although the vaginal mucosa may recover from doses of 20,000 to 25,000 r, lesser doses (10,000 to 15,000 r) can cause narrowing of the vagina due to perivaginal reaction. The rectovaginal septum will frequently not tolerate more than 6000 r ± (depending on the time-intensity factor and so forth). The bladder will tolerate slightly more than the rectum. It has been indicated that the mucosa of the bowel may not withstand doses much above 5000 r delivered in a short period of time; the muscularis and serosa of the bowel are rather more resistant.

The time in which the radiation is delivered is important. For example, it has been well demonstrated that in treating carcinoma of the skin, 2700 r given in one treatment has the same clinicobiologic effect as 4500 r given in five days.[39] Similar time-dose relations have been established for other tumors, particularly for carcinoma of the cervix.[8, 38, 40-42] The Strandqvist[42] fractionation diagram

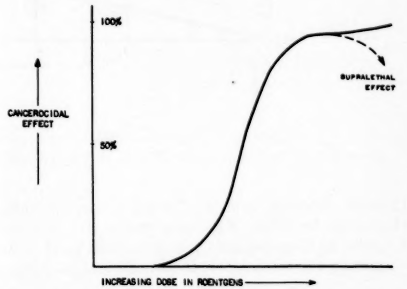

FIGURE 4. *An Approximate Estimate of the Relation between Dose and Lethal Effect for Carcinoma of the Cervix.*
The variations imposed by the time factor, fractionation, method of treatment and extent and histology of disease must be taken into account before attempting to assign definite dosage figures to the curve.

(Fig. 5) is widely used for the correlation of time and dose.

Tumor Dose versus Air or Skin Dose

In the day-to-day-practice of radiology, one becomes aware of the fact that not all physicians understand the methods of recording x-ray dosage. Most x-ray machines are calibrated in terms of the dose in air or to the skin at a certain distance, with a certain field size and so forth. This is the dose most commonly recorded from day to day on the usual x-ray treatment record. It should be realized that this does not necessarily represent the dose delivered to the tumor; that dose is calculated for the individual case and recorded separately. Figure 6 illustrates the discrepancy in air, skin and tumor

doses with the same geometry, for 200 kv and 2,000,000-volt therapy.

Figure 7 illustrates the necessity for avoiding the error of directly adding air or skin doses delivered

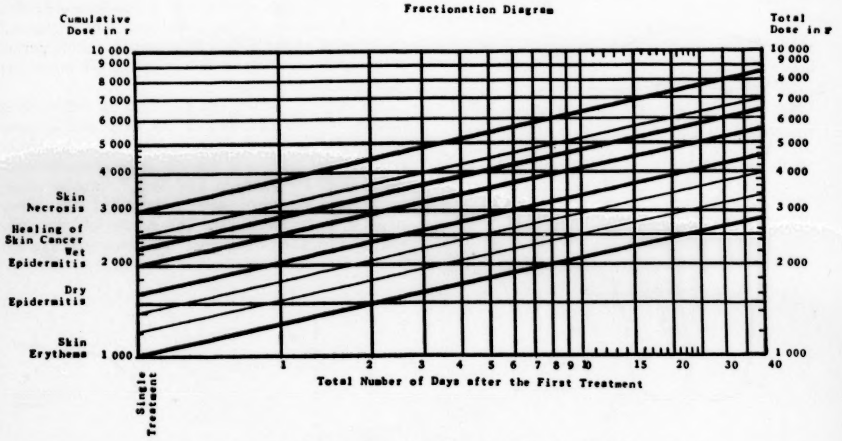

FIGURE 5. *Approximate Equivalent Roentgen Doses over Various Periods of Fractionation. Determinations are based on areas 20 to 30 sq. cm.* (*Reproduced from* Holmes and Schulz,[8] *by permission of the publisher.*)

through different portals. To paraphrase Schulz, this would be similar to adding the rainfall in New England to that in California when the object is to determine the water table in the Mississippi basin.

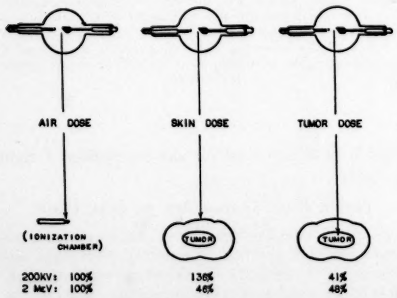

FIGURE 6. *Tumor Dosage.*

Ordinarily, tumor doses may be added directly. The terms "tumor dose," "depth dose" and "tissue dose" are often used interchangeably in a loose manner. "Integral" or "volume dose" is recorded in "gram-roentgens."

INTRACAVITARY AND INTERSTITIAL RADIATION

Good radiotherapy requires that the application of radium and x-ray or other sources of ionizing radiation be properly planned and integrated. Each modality has its own area of effectiveness, with a large overlapping of capabilities. It is not possible, therefore, to treat the disease (and the patient) properly unless one who is fully aware of the potentialities of both radium and x-ray plans the entire procedure from the beginning, in order that both

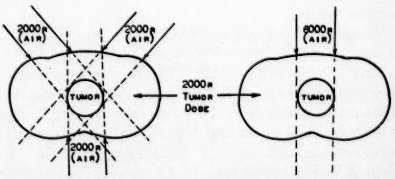

FIGURE 7. *Tumor Dosage.*

external and internal radiation may play their just parts, not conflicting with but complementing each other. Only by such integration will the method of therapy remain completely under control and yet be sufficiently flexible to meet and cope with the changing situation of individual response and reaction during treatment.

The older schools of radium treatment developed empirically, with later modifications. Today there

are two main schools of thought, each based on sound physical principles. One utilizes both intravaginal and intrauterine sources of radium; the other uses radium needles distributed uniformly throughout the tumor-bearing tissues of the pelvis.

Intracavitary Radium (Fig. 8)

In the *Paris* method initiated by Regaud[2, 8, 10, 37, 43-46] 66.6 mg. of radium is used, half being placed in the uterus and half in corks placed in the lateral fornices of the vagina. Occasionally a third cork is placed against the face of the cervix. The corks, held together by a metal spring, form an instrument called the colpostat. (In more recent times it has been demonstrated that the pressure of the spring will overcome the normal tensile strength of the vaginal wall, and the radium sources will frequently be laterally displaced by the end of twenty-four hours.) Five treatment days are required for this technic, with daily interruption for douching.

In the *Stockholm* method initiated by Heyman,[7, 37, 43, 44, 47] treatment is given fractionally — usually three treatments of twenty hours' duration spread over a total period of one month. Originally, the uterus contained 40 to 50 mg. and the vagina 60 to 75 mg. of radium; more recently the ratio of uterine to vaginal radium approaches a 1:1 ratio.[48] The actual type of applicators used varies according to the extent and shape of the tumor. Heyman and Kottmeier have made it clear that one outstanding reason for their success is that each treatment is individualized to the case. It is also interesting to note that in Sweden surgery is not used in any stage of the disease until radiation has been given a fair trial without sufficient success.

The *Manchester* system[2, 8, 10, 33-36, 44, 49] has been well described by Wilson[37]:

> Tod and Meredith have shown that it is possible, by arranging the radium in specially designed intracavitary applicators, to fix the relationship of the radium to certain important points within the pelvis so that the dose at these points can be pre-calculated. The vaginal radium is carried in rubber "ovoids" whose shape follows that of the isodose surface around the radium source contained within. The latter is 1.5 cm. long, and may contain 3, 4 or 5 "units" of radium according to whether the ovoid is small, medium or large. Similarly the intrauterine tube may be short, medium or long and contain 2 "units," 2 and 1 "unit" or 2, 2 and 1 "unit" of radium according to the length of the uterus. Thus by combinations of these radioactive foci, which depend upon the known dimensions of the vagina, etc., known dosage conditions may be set up.

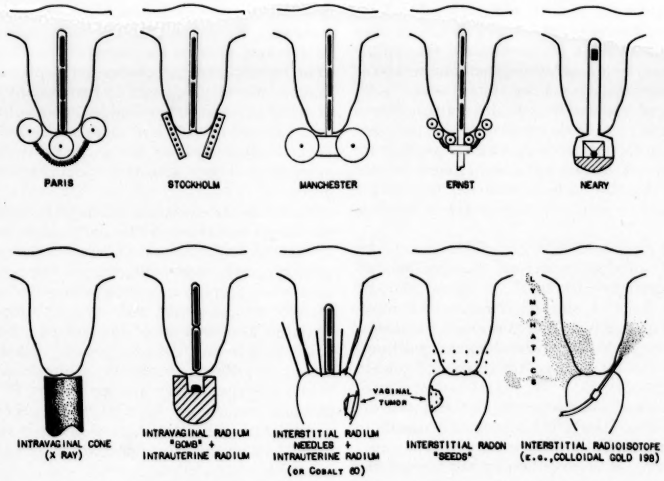

FIGURE 8. *Intracavitary and Interstitial Radiation.*

Many variations and improvements have been made on these "classical" technics, by both the originators and others. Fletcher[50] has added tungsten to the ends of plastic ovoids to offer more protection to the bladder and rectum with a relatively increased "lateral throw." Both Fletcher[50] and Silverstone[51] have added handles of individual design to the ovoids for stability of positioning as well as ease of handling. Campbell,[52] Ernst[2, 45, 53] and

Neary[2, 20, 54, 55] devised methods of fixing the intravaginal radium in constant relation to the intrauterine radium.

In the Ernst applicator, the radium sources are usually 10 mg. in each of four or six brass vaginal capsules and three 10-mg. radium sources in tandem in a brass intrauterine stem. The advantages of separation of the intravaginal sources are preferred by Ernst to the advantages of distance inherent in most ovoid systems.

Distance has been used to its fullest theoretical advantage in the Neary applicator. Two large radium sources (140 mg. each) are centrally placed in the vagina, being separated by a thick platinum shield so designed as to keep the dose tolerable in the immediate area, thus allowing a much greater dose at Point B relative to that at Point A. A massive platinum shield is placed beneath the radium to protect the rectum. Although originally placed in the uppermost portion of the uterus (as in Fig. 8), the 70 mg. of radium is now distributed over a greater length. Currently, this type of applicator is undergoing further revision after a preliminary clinical trial. A feature of some interest to the therapist is that the radium need not be inserted in the applicator until the applicator is fixed in place.

Relatively large quantities of radium are used for short periods of time in vaginal "radium bombs" in selected cases by Heyman.[7] A vaginal "bomb" designed by Bailey is used by Healy[44] with intrauterine radium. During the course of treatment, this bomb is placed in three different positions, being aimed toward each parametrium and toward the cervix.

In the hands of some expert radiotherapists, the intravaginal cone (x-ray)[56-60] is used with success in lieu of and occasionally in support of radium therapy. The intravaginal cone may be directed toward the cervix or the parametrium or both.

Interstitial Radium Needles

By "low-intensity" needles, less than 1.0 mg. of radium element per cm. of active length is usually meant. The idea of low-intensity needles was the result of a rather elementary observation. It was obvious that the use of short high-intensity radium sources of 10 to 100 mg. for any significant length of time produced an effect more easily accomplished by a hot cautery, whereas the desired effect of killing cancerous tissue without damaging normal structures was lacking. From the standpoint of pure physics, a uniform distribution of radium throughout any tumor would allow a generous cancerocidal dose with the least damage to normal structures. The answer then becomes clear: To utilize the radiation effect (as opposed to the cauterization effect) of radium, decrease the amount of each source to the point of normal tissue tolerance and increase the time of exposure to allow an adequate dosage to the tumor. One final refinement was to note the distribution of isodose curves around any linear radium source, and it became clear that to treat a tumor properly the field of radium implantation must extend beyond the physical boundary of the tumor. Hence, low-intensity needles as long as 6 cm. may be utilized in the treatment of carcinoma of the cervix.

In this country, the interstitial-needle method has been used to good advantage by Pitts and Waterman,[14, 15, 61] Arneson and Hauptman,[62, 63] Nolan and Quimby,[63] Martin,[44, 64, 65] Corscaden[66, 67] and many others. As with any other method of therapy, the technic varies according to the individual case and the individual therapist. However, an average set-up may be compared with fair accuracy. Nolan and Quimby[63] have produced, with painstaking work, comparisons of the Pitts–Waterman technic and the Arneson–Hauptman technic and a newly designed Nolan–Quimby method, planned to improve the isodose curves of the interstitial procedure. Each of these methods utilizes the natural uterine cavity for a comparatively larger amount of radium with consequent higher midfield doses.

Hare[68] treats carcinoma of the cervix as any other carcinoma elsewhere in the body might be treated by radium implantation. Therefore, he ignores the uterine cavity, simply distributing the needles with accurate and uniform spacing throughout the tumor, thereby claiming not only good therapeutic results but also, because of the lack of a heavy midline dose, a better "cosmetic result." Since approximately 50 per cent of carcinomas of the cervix occur before the age of fifty and since over 96 per cent of these women are married,[69] the prevention of vaginal narrowing and other sequelae is well worth the extra time and effort necessary to give a balanced treatment.

The accurate placement of radium sources in the female pelvis demands a skill not easily obtained; it requires an intimate knowledge of both the possible anatomic variations and the capabilities, both good and bad, of the radium sources used. Malpositioning of the needles may not only allow failure in controlling the tumor but may create "hot spots," which will lead to serious sequelae. Ernst has observed that unequal distribution of radium sources is as important as "radioresistance" in cases of failure to control disease.

Radon. Because of its physical properties, radon can be used as a complement to or substitute for radium therapy, although the radiobiologic properties of the two elements differ somewhat.[70] Radon "seeds" have the advantage that once properly placed they need not be removed. The larger the area to be implanted, the more difficult the accurate implantation of radon; hence, it is usually used in small tumors or when other means of radiation do not seem feasible. Even under ideal circumstances,

it is desirable to assay *each* "seed" to determine the actual amount of radon (in millicuries) present and to alter the geometric distribution accordingly. Dosage should be calculated in gamma roentgens and not recorded in terms of "millicurie hours" or "millicuries destroyed."

Cobalt.[60, 71-76] In very large amounts, cobalt^{60} is being used externally as the so-called cobalt bomb. In lesser amounts it can be utilized in a manner similar to radium. It may prove somewhat more flexible in application than radium, since it may be inserted into nylon tubing that has been prethreaded in a tumor. Cobalt^{60} may also be rendered magnetic in certain alloys and thus become easier to handle. It gives off no gaseous decay product (radon, a gas, is the daughter product of radium). However, the relatively shorter half-life of cobalt^{60} (5.3 years as opposed to 1590 years for radium) means that it will have to be recalibrated somewhat more frequently and returned to the nuclear reactor about every two or three years if treatment times are to remain similar.

Gold.[77-79, 198] The interstitial injection of radioactive colloidal gold into the cervix and parametrium represents a hypothetically intriguing new method of applying radiation. In addition to the radiation effects at the sites of injection, the colloidal particles are picked up by the lymphatics and transported to lymph nodes, where radiation effects have been observed.

The possible applications of radioactive chromic phosphate, radiozinc gel and many other radioisotopes in various physical and chemical states are being investigated in many quarters.[78, 80]

External Radiation

The sphere of effectiveness of radium in treatment of carcinoma of the cervix is limited. Any disease beyond the cervix and immediately adjacent tissues must be additionally irradiated by other means if tumor control is to be accomplished.

External radiation therapy may be given singly or in support of radiation that may have been delivered to the cervix through the vagina. Although the usual instrument of external radiation is the x-ray machine, "radium bombs," "cobalt bombs" and "radio-iridium bombs" have been and are being used for this purpose. The advent of the nuclear reactor has allowed the construction of the "cobalt bomb" and may well allow the use of other radioisotopes in large quantities.

The most commonly available deep-therapy apparatus is in the 200-250 kv range. To deliver with this voltage an adequate tumor dose to the pelvis in other than a thin patient requires skill and ingenuity. With 400 kv, tumor doses of 6000 r or more can be delivered to the pelvis by utilizing multiple portals and compression.

In the supervoltage range (800 kv and above), delivery of an adequate tumor dose becomes somewhat simpler, as the depth dose increases and the skin dose decreases.[12, 81-84] The skin is no longer the limiting factor, being replaced in that "function" by the bowel. The differential absorption in bones and soft tissues is negligible; this should indicate an even lower incidence of radionecrosis of the hip. (This comparatively rare possibility can often be avoided at lower voltage through proper technics.) "Radiation sickness" occurs with less frequency at these higher voltages.[85]

The use of multiple portals has been carried to its extreme by rotation therapy. Although rotation may be relatively more important at lower voltages, it is being used in the supervoltage range with considerable initial success.[86, 87]

In planning external radiation that is complementary to radium (or other internal radiation), the fields must be so designed as to avoid those areas that received tumorocidal doses. Those areas that have received less than tumorocidal doses from internal sources are given external therapy in amounts sufficient to raise the total dose to the proper level. This may mean that the lateral portions of the pelvis receive most of the dose by external means, whereas the medial portions receive most of the dose by internal means.

The Radiation Physicist

In Europe, particularly, the radiation physicist has become an accepted member of the radiologic team. Although this is not a direct analogy, the physicist is as necessary to the radiologist as the anesthetist is to the surgeon. Although the one can work if necessary without the other, the patient's best interests demand that the two work as a team. Just as many of the advances in surgery can be attributed to improve anesthesia, so many of the advances in radiotherapy are attributable to improved physics. The radiation physicist, through his expert knowledge of physics and mathematics, is often able to point out easier and more accurate methods of therapy. He is quick to spot the fallacies of improper or inadequate treatment. In short, he keeps radiotherapy on a sound physical basis while allowing the radiologist more time for the clinical management of the patient.

The Evaluation of Radiation Therapy

The evolution of radiation therapy at the Massachusetts General Hospital may be cited as an example of why critical evaluation of past results have been difficult. Prior to 1948 the general policy was that the radiologist was in charge of external radiation only, and a detailed attempt at accurate correlation of radium and x-ray therapy was not made. Radium was applied by many different surgeons, and the dosage was recorded only in terms of "milligram hours." The geometric distribution and the time factor were not considered in detail. Roentgenograms made after radium application, if taken,

were not utilized in calculations. These facts preclude any accurate evaluation of the results obtained.

For the past two and a half years, a modification of the Manchester "ovoid" technic in combination with supervoltage radiation has been utilized. The early results appear to be satisfactory. After the patient has been accepted for radiation therapy, the over-all treatment is planned by the radiologist and the gynecologist in consultation. Execution of the radium treatment is carried out by the joint efforts of the radiologist and the gynecologist. After the application of radium, opaque media are placed in the vagina, bladder and rectum, and appropriate precision roentgenograms are made. From these, three-dimensional reconstructions are built and the actual dosage is determined. Radium therapy is usually delivered in two applications, separated by an interval of ten days to two weeks. External radiation is given concurrently and completed after the application of radium. From the precision roentgenograms the proper radium isodose is determined, and the external radiation field is adjusted around this insofar as possible. This as a rule means that an inverted U-shaped field is treated by supervoltage technics. Rotation or semirotation technics with wedge-shaped filters in the lateral fields may be utilized in the near future. A tissue dose to the midplane of the pelvis through Point A of 6000± r in five weeks is attempted. This particularly applies to Stages I and II. In the later stages the problem of correlation of the several modalities used is not so complex; external radiation alone is often given.

The results of this approach to radiation therapy in carcinoma of the cervix appear promising, although sufficient time has not elapsed to warrant any definite conclusions. The most encouraging aspect is the obvious benefit to the patient that results from a program of intimate co-operation between gynecologist and radiologist. In a recent article on the surgical treatment of carcinoma of the cervix, Meigs[88] makes two significant concluding statements concerning proper evaluation of surgical therapy that seem equally applicable to evaluation of radiation therapy:

> It is not fair to criticize a procedure if the procedure is not carried out properly. . . . Lack of knowledge and ability should not condemn a good procedure but shows ignorance on the part of those directing the attack on the disease.

Summary

Until (and perhaps after) comparable series of surgically and radiologically treated cases of carcinoma of the cervix exist, radiation therapy should be considered the treatment of choice.

"Palliative" should not be confused with "curative" therapy.

Radiosensitivity and radiocurability are not synonymous.

Metastatic disease in lymph nodes can be clinically controlled by radiation in many cases.

Although useful in intermediate calculations, the term "milligram hours" should not be used as an expression of dosage. The *roentgen* is the accepted measure of dosage.

Radon and radioisotope therapy can and should be calculated in *roentgens*. The use of "millicurie hours" and "millicuries destroyed" as a final expression of dosage should be avoided.

The time and manner in which the treatment is delivered greatly affect the number of roentgens necessary to produce a given clinicobiologic response.

Radium and x-ray are essentially the same modality. Good radiotherapy requires the proper integration of all sources of radiation.

The correct application of radium requires not only a knowledge of anatomy and pathology but an equally well founded knowledge of physics and radiobiology.

Therapy received should be expressed primarily in terms of *tumor dose*. The addition of *air* and *skin dose* through different portals of entry is to be avoided, as this has no meaning.

The radiation physicist is an important member of the radiologic group.

Precise determination of physical factors is mandatory for the proper evaluation of radiation therapy.

Close co-operation by gynecologist and radiologist is imperative.

References

1. Schmitz, H. E., Towne, J. E., and Smith, C. J. Role of surgery in management of cervical carcinoma. *Radiology* **57**:826-831, 1951.
2. Nolan, J. F., Costolow, W. E., and DuSault, L. Radium treatment of carcinoma of cervix uteri. *Radiology* **54**:821-831, 1950.
3. Henriksen, E. Surgical treatment of cancer of cervix. *Radiology* **54**: 819-821, 1950.
4. Cade, S. *Malignant Disease and Its Treatment by Radium.* 1280 pp. Baltimore: Williams and Wilkins Company, 1940.
5. *Cancer Bulletin.* Edited by R. L. Clark, Jr. **1**:79, 84, 85 and 93, 1949.
6. Fletcher, G. H. Planning of external irradiation in pelvic cancer. *Am. J. Roentgenol.* **64**:95-113, 1950.
7. Heyman, J. Improvement of results in treatment of uterine cancer. *J. A. M. A.* **135**:412-416, 1947.
8. Holmes, G. W., and Schulz, M. D. *Therapeutic Radiology.* 347 pp. Philadelphia: Lea and Febiger, 1950.
9. O'Brien, F. W. Radium treatment of cancer of cervix: historical review: Janeway memorial lecture. *Am. J. Roentgenol.* **57**:281-297, 1947.
10. Paterson, R. *Treatment of Malignant Disease by Radium and X-Rays.* 622 pp. Baltimore: Williams and Wilkins Company, 1948.
11. Richards, G. E. Analysis of technical factors and results of treatment in carcinoma of cervix uteri: description of improved radium applicator. *Am. J. Roentgenol.* **58**:783-797, 1947.
12. Schmitz, H. E. Treatment of cervix carcinoma with radium and 800 kilovolt x-ray. *Am. J. Obst. & Gynec.* **55**:262-272, 1948.
13. *Tumor Topics.* Edited by R. L. Clark, Jr., and R. W. Cumley. Houston: Medical Arts Publishing Foundation, 1950.
14. Waterman, G. W., DiLeone, R., and Tracy, E. Use of long interstitial radium needles in treatment of cancer of cervix. *Am. J. Roentgenol.* **57**:671-678, 1947.
15. Waterman, G. W., and Reid, W. A. Place of deep external x-ray irradiation in treatment of carcinoma of cervix by long element needles. *Radiology* **52**:34-40, 1949.
16. Heyman, J., Donaldson, M., and Scheffey, L. C. *Annual Reports on Results of Radiotherapy in Cancer of Uterine Cervix.* Stockholm, 1949.
17. Glücksmann, A. Relation of radiosensitivity and radiocurability to histology of tumour tissue. *Brit. J. Radiol.* **21**:559-566, 1948.
18. *Idem.* Role of tumour bed in treatment of squamous-cell cancers by irradiation. *J. Obst. & Gynaec. Brit. Emp.* **57**:322-327, 1950.
19. *Idem.* Preliminary observations on quantitative examination of human biopsy material taken from irradiated carcinomata. *Brit. J. Radiol.* **14**:187-198, 1941.
20. Donaldson, M. Future in treatment of carcinoma of cervix. *J. Obst. & Gynaec. Brit. Emp.* **57**:411-414, 1950.
21. Glücksmann, A., and Way, S. On choice of treatment of individual carcinomas of cervix based on analysis of serial biopsies. *J. Obst. & Gynaec. Brit. Emp.* **55**:573-582, 1948.
22. Graham, R. M. Effect of radiation on vaginal cells in cervical carcinoma. *Surg., Gynec. & Obst.* **84**:153-173, 1947.

23. Graham, R. M., and Meigs, J. V. Value of vaginal smear. *Am. J. Obst. & Gynec.* **58**:843-850, 1949.
24. Sturgis, S. N., DeMuylder, E., and Meigs, J. V. Uptake of labelled phosphorus by cancer of cervix: preliminary report. *Ann. Surg.* **133**:305-312, 1951.
25. Morton, D. G. Surgical treatment of cervical cancer: Wertheim operation: pelvic lymphadenectomy. *Am. J. Roentgenol.* **57**:685-696, 1947.
26. Wood, C. A. P. Some factors influencing response of cancer to radiation. *J. A. M. A.* **140**:513-520, 1949.
27. McGregor, L. Reactions to radiation in lymph nodes containing carcinoma metastases of squamous cell type. *Acta radiol.* **15**:129-152, 1934.
28. Brown, W. E., Meschan, I., Kerekes, E., and Sadler, J. M. Effect of radiation on metastatic pelvic lymph node involvement in carcinoma of cervix. *Am. J. Obst. & Gynec.* **62**:871-889, 1951.
29. Henriksen, E. Lymphatic spread of carcinoma of cervix and of body of uterus: study of 420 necropsies. *Am. J. Obst. & Gynec.* **58**:924-942, 1949.
30. *Idem.* Dispersion of cancer of cervix. *Radiology* **54**:812-815, 1950.
31. Maxfield, J. R., Jr., McIlwain, A. J. Diagnostic value of pneumoperitoneum. *Radiology* **42**:346-355, 1944.
32. Kerekes, E. S., and Meschan, I. Radium therapy of carcinoma of cervix uteri: method of dosimetry affording complete description of physical factors. *Radiology* **56**:719-730, 1951.
33. Tod, M. C. Optimum dosage in treatment of carcinoma of uterine cervix by radiation. *Brit. J. Radiol.* **14**:23-29, 1941.
34. *Idem.* Optimum dosage in treatment of cancer of cervix by radiation. *Acta radiol.* **28**:564-575, 1947.
35. *Radium Dosage: The Manchester system.* Edited by W. J. Meredith. 124 pp. Baltimore: Williams and Wilkins Company, 1947.
36. Meredith, W. J. Dosage distribution and dosage in carcinoma of uterine cervix. *Radiology* **54**:386-391, 1950.
37. Wilson, C. W. *Radium Therapy: Its physical aspects.* 224 pp. London: Chapman and Hall, Ltd., 1945.
38. Paterson, E., and Thompson, M. V. Time-intensity factors in x-irradiation. *Brit. J. Radiol.* **21**:414-419, 1948.
39. Hale, C. H., and Holmes, G. W. Carcinoma of skin: influence of dosage on success of treatment. *Radiology* **48**:563-569, 1947.
40. Lea, D. E. Theory of action of radiations on biological materials capable of recovery: time-intensity factor. *Brit. J. Radiol.* **11**: 489-497, 1938.
41. Martin, C. L. Time factor in radiation therapy. *Am. J. Roentgenol.* **59**:1-8, 1948.
42. Strandqvist, M. *Acta radiol.* Supp. **55**:1944. Table 18.
43. Ernst, E. C. Intracavitary radium for cancer of cervix. In *Clinical Therapeutic Radiology.* Edited by U. V. Portmann. 748 pp. New York: Thomas Nelson and Sons, 1950. Pp. 361-392.
44. Martin, C. L. Radiation therapy in diseases of female genital organs. In *Clinical Radiation Therapy.* Edited by E. A. Pohle. 902 pp. Philadelphia: Lea and Febiger, 1950. Pp. 300-490.
45. Sandler, B. Investigation into dosage delivered by certain techniques in radiation therapy of carcinoma cervix. *Brit. J. Radiol.* **11**:623-636, 1938.
46. *Idem.* Radium distribution factor in carcinoma cervix therapy with comparison of techniques. *Brit. J. Radiol.* **14**:284-293, 1941.
47. Kottmeier, N. L. Unpublished data.
48. *Idem.* Personal communication.
49. Tod, M. C., and Meredith, W. J. Dosage system for use in treatment of cancer of uterine cervix. *Brit. J. Radiol.* **11**:809-824, 1938.
50. Fletcher, G. H. Personal communication.
51. Silverstone, S. M., Harris, W., and Greenberg, M. Radium therapy for cancer of cervix uteri with new type of colpostat. *Am. J. Roentgenol.* **67**:294-299, 1952.
52. Campbell, L. A. Carcinoma of cervix: applicator for greater parametrial dosage. *Am. J. Roentgenol.* **57**:697-702, 1947.
53. Ernst, E. C. Probable trends in irradiation treatment of carcinoma of cervix uteri with improved expanding type of radium applicator. *Radiology* **52**:46-62, 1949.
54. Neary, G. J. Physical aspects of intracavitary radium treatment of carcinoma of cervix uteri. *Brit. J. Radiol.* **16**:225-233 and 263-269, 1943.
55. *Idem.* Physical aspects of intracavitary radium treatment of carcinoma of cervix uteri: new applicator. *Brit. J. Radiol.* **20**:454-469, 1947.
56. Ackerman, L. V., and del Regato, J. A. *Cancer: Diagnosis, treatment, and prognosis.* 1115 pp. St. Louis: C. V. Mosby Company, 1947.
57. del Regato, J. A. Transvaginal roentgen therapy in carcinoma of cervix. *Radiology* **49**:413, 1947.
58. *Idem.* Treatment of carcinoma of cervix. *Radiology* **46**:579-582, 1946.
59. Caulk, R. M. Transvaginal roentgen therapy. In *Clinical Therapeutic Radiology.* Edited by U. V. Portmann. 748 pp. New York: Thomas Nelson and Sons, 1950. Pp. 343-348.
60. Twombly, G. H., and Chamberlain, J. A. Intravaginal roentgen therapy in cancer of cervix uteri. *Radiology* **52**:14-25, 1949.
61. Waterman, G. W., and Tracy, E. M. Complications following use of low intensity, long radium element needles in treatment of cancer of cervix uteri. *Am. J. Roentgenol.* **60**:788-794, 1948.
62. Arneson, A. N., and Hauptman, H. Radium needles in treatment of carcinoma of cervix and vagina. *South M. J.* **33**:286-293, 1940.
63. Nolan, J. F., and Quimby, E. H. Dosage calculation for various combinations of parametrial needles and intracervical tandems. *Radiology* **40**:391-402, 1943.
64. Martin, C. L. New developments in irradiation therapy of cancer of uterine cervix. *Texas State J. Med.* **44**:587-593, 1948.
65. *Idem.* Elimination of irradiation sequelae in treatment of cancer of cervix uteri. *Proc. Third Am. Cong. Obst. & Gynec.*, 1947.
66. Corscaden, J. A., Gusberg, S. B., and Dolan, C. P. Precision dosage in interstitial irradiation of cancer of cervix uteri. *Am. J. Roentgenol.* **60**:522-534, 1948.
67. Corscaden, J. A. Interstitial radium therapy for cancer of uterine cervix. In *Clinical Therapeutic Radiology.* Edited by U. V. Portmann. 748 pp. New York: Thomas Nelson and Sons, 1950. Pp. 349-360.
68. Hare, H. F. Personal communication.
69. Morris, J. M., and Meigs, J. V. Carcinoma of cervix: statistical evaluation of 1,938 cases and results of treatment. *Surg., Gynec. & Obst.* **90**:135-150, 1950.
70. Love, W. H. On relative biological effect produced by equal radiation doses from radium and from radon. *Brit. J. Radiol.* **11**:46-64, 1938.
71. Meschan, I., Edwards, R. R., and Rosenbaum, P. J. Practical physical aspects in use of radioactive cobalt^{60} as radium substitute. *Am. J. Roentgenol.* **65**:255-264, 1951.
72. Morton, J. L., Barnes, A. C., Callendine, G. W., Jr., and Myers, W. G. Individualized interstitial irradiation of cancer of uterine cervix using cobalt^{60} in needles, inserted through lucite template. *Am. J. Roentgenol.* **65**:737-748, 1951.
73. Myers, W. G. Applications of artificially radioactive isotopes in therapy: cobalt.^{60} *Am. J. Roentgenol.* **60**:816-823, 1948.
74. Morton, J. L., Callendine, G. W., Jr., and Myers, W. G. Radioactive cobalt^{60} in plastic tubing for interstitial radiation therapy. *Radiology* **56**:553-560, 1951.
75. Wilson, C. W. Radiocobalt (CO^{60}) as therapeutic alternative to radium. *Am. J. Roentgenol.* **65**:726-736, 1951.
76. Editorial. Cobalt^{60} as source for radiotherapy. *Radiology* **58**:113, 1952.
77. Sherman, A. I., Bonebrake, M., and Allen, W. M. Application of radioactive colloidal gold in treatment of pelvic cancer. *Am. J. Roentgenol.* **66**:624-638, 1951.
78. Tabern, D. L., Taylor, J. D., and Gleason, G. I. Radioisotopes in pharmaceutical and medical studies. *Nucleonics* **7**:3-23, 40-55, 1950 and **8**:60-70, 1951.
79. Chamberlain, R. H., Klingensmith, P. O., and Hale, J. Unpublished data.
80. Low-Beer, B. V. A. *Clinical Use of Radioactive Isotopes.* 414 pp. Springfield: Charles C Thomas, 1950.
81. Schmitz, H. E. Further study of supervoltage x-ray therapy in carcinoma of cervix. *Radiology* **40**:458-462, 1943.
82. Trump, J. G., and Cloud, R. W. Production and characteristics of 3,000 kilovolt roentgen rays. *Am. J. Roentgenol.* **49**:531-535, 1943.
83. Trump, J. G., Moster, C. R., and Cloud, R. W. Efficient deep tumor irradiation with roentgen rays of several million volts. *Am. J. Roentgenol.* **57**:703-710, 1947.
84. Trump, J. G. Physical basis for high skin tolerance of super-voltage roentgen rays. *Radiology* **50**:649-655, 1948.
85. Robbins, L. L., and Schulz, M. D. Supervoltage radiation in gynecology. In *Progress in Gynecology.* Edited by J. V. Meigs and S. H. Sturgis. Vol. 2. 820 pp. New York: Grune and Stratton, 1950. Pp. 610-621.
86. Trump, J. G., Wright, K. A., Evans, W. W., Hare, H. F., and Lippincott, S. W., Jr. Two million volt roentgen therapy using rotation. *Am. J. Roentgenol.* **66**:613-623, 1951.
87. Hare, H. F., et al. Physical and clinical aspects of supervoltage rotational therapy. *Radiology* **57**:157-168, 1951.
88. Meigs, J. V. Radical hysterectomy with bilateral pelvic lymph node dissection: report of 100 patients operated on five or more years ago. *Am. J. Obst. & Gynec.* **62**:854-870, 1951.

MEDICAL INTELLIGENCE

PNEUMOCHOLECYSTITIS*

Report of a Case

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PNEUMOCHOLECYSTITIS (a term coined by Heifetz and Senturia[1]) describes gas in the gall bladder with associated infection. It may be present within the lumen, in the wall or both. Gas within the gall bladder or biliary tree is a not too uncommon finding at present, as a result of the increasingly routine use of the roentgen ray. Gas may gain access to the biliary tree in one of three ways: fistulous communication between the gall bladder or biliary tree with some portion of the gastrointestinal tract — this fistula may result from an inflammatory process or be secondary to a surgical procedure such as choledochoenterostomy or cholecystoenterostomy; incompetence of the sphincter of Oddi — which may be intrinsic or secondary to a surgical procedure such as sphincterotomy; and gas within the gall bladder due to infection by gas-forming organisms. The latter category is the most uncommon of the three; its rarity is more evident in view of the fact that only approximately 22 authenticated cases have been reported,[2-5, 7-12, 14] with the case herewith reported bringing the total to 23.

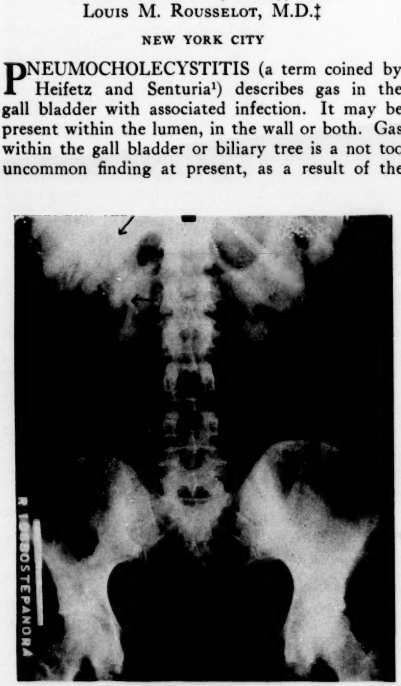

Figure 1. *Flat Plate of Abdomen, Showing Gas-Filled Lumen of the Gall Bladder, With Gas Also in the Wall.*

Lobingier[13] is usually given credit for first recognizing this entity (1908); Hegner[3] was the first (1931) to make the preoperative diagnosis. The diagnosis, which may be established with a plain film of the abdomen, rests on the pathognomonic role of the roentgenogram.

Case Report

L. S., a 44-year-old woman, was admitted with a history of 6 days' right-upper-quadrant pain associated with vomiting, fever and anorexia. There was no previous history of abdominal pain or indigestion. On the day of admission it was noted that vomiting had ceased and only minimal abdominal pain was present.

The temperature was 102°F., the pulse 100 and the blood pressure 145/80. The patient did not appear acutely ill.

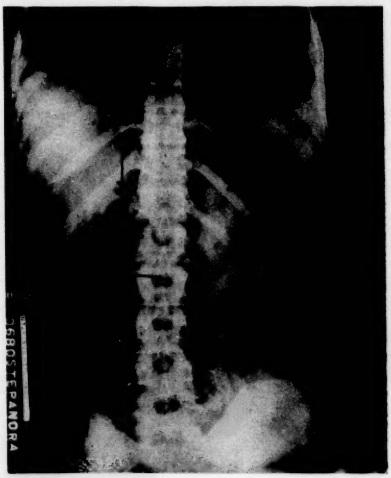

Figure 2. *Upright Film, Demonstrating Fluid Level.*

The significant physical findings were limited to the abdomen, which was flat and was soft throughout, with a large palpable ovoid 15-by-6-cm. tender mass in the right upper quadrant that descended with respirations.

Laboratory examination of the blood revealed a white-cell count of 19,800, with 96 per cent neutrophils. Examination of the urine was negative. The blood sugar was 94, the urea nitrogen 10 and the serum amylase 71. A chest plate revealed an elevated right diaphragm with a small amount

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of fluid at the base. Flat and upright films of the abdomen (Fig. 1 and 2) demonstrated a gas pocket with fluid levels in the right upper quadrant. There was also gas outlining the soft-tissue planes of an oval mass measuring approximately 13 cm. in length. Barium-enema examination and gastrointestinal series revealed no communication of the intestinal tract with this mass. A diagnosis of pneumocholecystitis was made at this time.

The patient was prepared for surgery in the usual manner, including the addition of vigorous biotherapy. At operation an acutely inflamed, distended gall bladder was found, with a localized pericholic abscess (culture of which was negative), obliteration of the cystic duct and myriad small bilirubin stones. The patient's postoperative course was uneventful. Aerobic and anaerobic cultures of the gall bladder contents revealed no organisms.

Summary

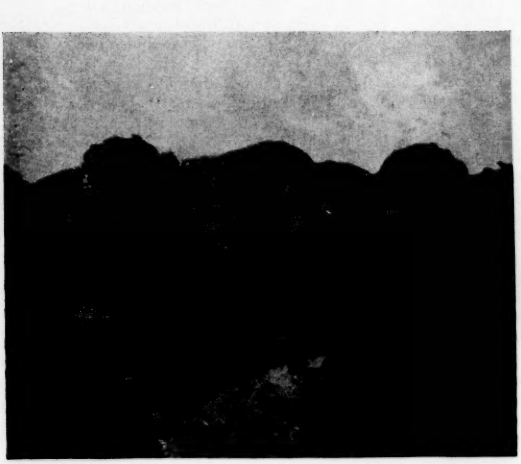
An unusual case of gas within an inflamed gall bladder is presented. This condition has been termed "pneumocholecystitis" by Heifetz and Senturia.

A plain scout film of the abdomen is usually pathognomonic of this entity.

This represents the twenty-third reported case in the literature, with an over-all mortality of approximately 13 per cent.

References

1. Heifetz, C. J., and Senturia, H. R. Acute pneumocholecystitis. *Surg., Gynec. & Obst.* **86**:424-433, 1948.
2. Kirchmayr, L. Gas gangrene of gallbladder in elderly man. *Zentralbl. f. Chir.* **52**:1522-1527, 1925.
3. Hegner, C. F. Gaseous pericholecystitis with cholecystitis and cholelithiasis. *Arch. Surg.* **22**:993-1000, 1931.
4. Simon, J. Le pyopneumocholécyste et son diagnostic radiologique. *Presse méd.* **40**:1938-1940, 1932.
5. del Campo, J. C., and Otero, J. P. Neumatoxis espontánea de las vías biliares. *Arch. urug. de med., cir. y especialid.* **17**:341-350, 1940.
6. Stevenson, C. A. Emphysematous cholecystitis. *Am. J. Roentgenol.* **51**:53-60, 1944.
7. Schmidt, E. A. Emphysematous cholecystitis and pericholecystitis. *Radiology* **31**:423-427, 1938.
8. McCorkle, H., and Fong, E. E. Clinical significance of gas in gall bladder. *Surgery* **11**:851-868, 1942.
9. Pierini, A. Gangrena gaseosa de la vesícula biliar: consideraciones clínico-radiológicas. *Dia méd.* **17**:988-994, 1945.
10. Tanner, E. K. Acute gas-production cholecystitis. *Surg., Gynec. & Obst.* **32**:468, 1921.
11. Wybauw, L. Image vésiculaire inhabituelle, *J. belge gastroenterol.* **4**:123-125, 1936.
12. Friedman, J., Aurelius, J. R., and Rigler, L. G. Emphysematous cholecystitis. *Am. J. Roentgenol* **62**:814-822, 1949.
13. Lobingier, A. S. Gangrene of gall bladder. *Ann. Surg.* **48**:72, 1908.
14. Retterbush, W. C., Fishman, M. B., Baird, W. A., and Collins, J. I. Emphysematous cholecystitis: report of case with successful treatment. *Ann. Surg.* **134**:268-276, 1951.



Massachusetts Physicians Art Association

4. *The Tar Paper House*

(Third Prize, American Medical Association Exhibit, Atlantic City, 1951)

Painting in Oil by

Elizabeth Z. Kleinman, M.D.

Assistant in Department of General Practice

New England Hospital

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38171

PRESENTATION OF CASE

First admission. A nineteen-year-old boy was admitted to the hospital because of diarrhea.

For the eight years preceding admission the patient had numerous bowel movements, averaging 8 to 10 during the day and 3 to 5 at night, accompanied by urgency and tenesmus. The stools were usually loose, light brown and particulate. Occasionally they were watery; they sometimes contained blood and sometimes fragments of undigested food. The diarrhea was made worse by emotional factors and by exercise. He had been treated with iron, arsenic and tonics with no change in the symptoms. He had not followed a prescribed diet but had learned from experience to avoid the foods that aggravated the diarrhea. He had had no cramps, fever, chills, nausea or vomiting. He felt generally weak and listless, had a poor appetite and was underweight. Since the onset of the diarrhea there had been no remissions; the disability due to this had not interfered with his schooling but had interfered with his getting a job.

Physical examination revealed a tall undernourished boy in no distress who showed a normal concern about his disease. The examination was negative except for the rectal examination; the anus was tender, and less than one finger's length in the canal was a stricture that would not allow the passage of one finger and that gave the impression of being caused by a fibrous band.

The temperature was 99°F., the pulse 80 and the respirations 20. The blood pressure was 118 systolic, 78 diastolic.

Examination of the blood revealed a hemoglobin of 80 per cent, a red-cell count of 5,000,000 and a white-cell count of 13,000, with 58 per cent neutrophils. The nonprotein nitrogen was 20 mg. and the serum protein 7.4 gm. per 100 cc.; the chloride was 95.8 milliequiv. and the carbon dioxide 26.3 milliequiv. per liter. The urine was normal. The stools gave a positive guaiac reaction; cultures of the stool were negative. A Frei test and a formol-gel test were negative. On proctoscopic examination the instrument could be introduced only a few inches and revealed a narrowed red-streaked lower rectum into which watery pus welled. The mucosa was thickened and granular and bled on moderate trauma. There were a few definite ulcers about 2 mm. in diameter. A swab from one was negative for ameba. Barium-enema examination showed no delay in passage of barium to the cecum. There was a complete loss of haustral markings throughout the entire colon and ragged mucosal edges indicative of multiple small ulcerations, most marked in the transverse, descending and sigmoid colon. There was a constricted area in the hepatic flexure. The cecum was smaller than usually seen and was ulcerated. The ileocecal valve was patent, and the passage of barium into the terminal ileum showed a definite ulcerated appearance in the distal 12 to 15 inches of the ileum. A gastrointestinal series confirmed the findings in the lower ileum but was otherwise negative.

On the eleventh day an ileostomy was performed 2.5 feet proximal to the ileocecal valve; at operation the entire colon, the cecum and the distal 2 feet of ileum were thickened and contracted. He did well postoperatively, gained weight rapidly and was discharged on the twenty-third day.

Second admission (thirteen years later — at the age of thirty-two) because of foul bloody stools.

For one year following his operation he had some difficulty with skin infection and some rectal bleeding, but this subsided gradually. He was able to work full time, did not have to restrict his activities, gained weight until he weighed 235 pounds, married, had a family and generally led a normal life. His bowel movements per rectum consisted of one or two shreds of mucus per month, until six months prior to admission when rather suddenly he had 3 very foul bloody movements per rectum. From then on he had 2 to 3 of these each week. There had been no known emotional or psychic disturbance. There was no associated weight loss or loss of well-being. The ileostomy continued to function normally. A barium-enema examination five months prior to entry showed the patient unable to tolerate even 200 cc. of the fluid, and adequate filling of the large bowel could be accomplished only to the splenic flexure. The visualized portion of the large bowel, including the rectum, was severely reduced in caliber and showed slightly irregular margins and a markedly thickened wall.

The physical examination was generally negative. The rectal sphincter was too spastic to admit the examining finger. No fistulous tracts were noted.

The temperature, the pulse, the respirations and the blood pressure were normal.

Laboratory examination revealed a hemoglobin of 11 gm. and a white-cell count of 11,600. The urine and prothrombin time were normal.

On the second day an operation was performed.

Differential Diagnosis

Dr. Daniel S. Ellis*: I do not know why Dr. Castleman gave me this case: Either I am in the dark completely about what was going on here or this is a perfectly straightforward story and course of ulcerative colitis.

I should like to point out that although the patient had had ulcerative colitis for at least eight years, — and from the appearance of the x-ray films he may have had it much longer, — he did not have surgery during adolescence. It is desirable, whenever possible, to delay surgery until young patients have their growth and are more or less developed. The surgery is tolerated better and the ileostomy is accepted better by the older patient than by the adolescent.

The x-ray picture is classical of a chronic, indolent, slowly advancing type of disease that is known to have lasted for eight years and probably much longer. The differential diagnosis at the time of the first admission was tuberculosis, chronic amebiasis and chronic bacillary dysentery, all of which seem to have been ruled out as well as anyone could rule them out. It is well recognized that an ulcerative colitis of specific etiology is occasionally missed, but certainly these conditions were considered and were eliminated at the time of the first admission.

The rectal stricture is one complication of the ulcerative colitis. It may commonly follow perirectal sepsis, which this patient apparently had not had, or it may develop in the normal course and progression of the disease. A Frei test, which is a relatively accurate test as such skin tests go, was done to rule out lymphogranuloma inguinale, and I think I can dismiss that cause of stricture. I assume that at the time of operation there was no evidence of a neoplastic process but that there was fibrotic narrowing.

The ileostomy was done with dramatic effect. Having been a malnourished semi-invalid, this patient apparently bloomed after the ileostomy, put on weight, became a useful citizen, became a father and had done a good job of contributing to society. He might have gone on for a number of years without an ileostomy, but he certainly would not have been this type of person without an ileostomy. That, we in this hospital believe, is one of the real virtues of an ileostomy for these patients who do not get well on a medical program.

The rectal stricture that admitted the examining finger and sigmoidoscope with difficulty is a formidable deterrent and an obstacle in the proper following of such patients. There was no indication in the record whether this patient became so well that he no longer sought medical care or whether he was under constant medical care during the whole interval between the first and second admissions. I think that he may have been so well that he stayed away from physicians until he got into trouble. If that is true, it is too bad. No patient with ulcerative colitis and an ileostomy, whose colon is left in place, should go without medical surveillance for any long period of time. According to several sets of statistics on carcinoma in patients with chronic ulcerative colitis, the incidence varies somewhere between 2 and 7 per cent. When these statistics are put together, the average incidence of cancer in the colon is probably about 5 per cent in patients who have chronic idiopathic ulcerative colitis.

Dr. Frank C. Wheelock: He did not see physicians during that period.

Dr. Ellis: That is a tribute to the effectiveness of ileostomy. He was so well and so fortunate in having no trouble with the ileostomy that he did not need a physician. When he did come back, he had a very important change, according to my way of thinking — namely, that having had one or two rectal discharges at relatively infrequent periods, he suddenly began to have frequent rectal discharges of bloody pus. This is a very serious change that must be investigated without further delay. How can you investigate this patient? One cannot feel very far in the rectum; one cannot look very far into the rectum with any lighted instrument, so the x-ray examination is the only real means of trying to find out what was going on. Dr. Wyman, may we see these films?

Dr. Stanley M. Wyman: As Dr. Ellis said, it was impossible to do a local visual examination, and apparently we were unable to do a good examination by barium enema. This examination shows the column of barium extending only to the region of the splenic flexure and is totally inadequate. The bowel is seen to be quite thickened; the wall can be made out well in this portion of the film. The lumen is greatly reduced in caliber, and there is loss of normal mucosal pattern with fine granular texture suggesting replacement of the mucosa by the ulcerating process. I can say nothing about a possible filling defect.

Dr. Ellis: Do you think that is the full extent of the lumen?

Dr. Wyman: I do not think so; in other films we have considerably better filling, and it amounts to 4 to 5 mm. in diameter.

Dr. Ellis: Certainly the lumen is markedly narrowed. The fact that one sees no neoplastic lesion or mass from the anal orifice up to the splenic flexure does not rule out the possibility that one is there. That the barium did not go farther in the splenic flexure may be due to an obstructing neoplastic lesion or fibrosis with a stricture.

*Assistant physician, Massachusetts General Hospital.

I believe that the sudden onset of change in rectal discharge, the increase in quantity, the increase in frequency and the bloody nature of it are strongly indicative of neoplasm. Just where it was I do not know. It may have been located anywhere from the anal orifice to the cecum. I think he was operated on with the idea of resecting the colon, which should have been taken out a long time ago. At operation, malignant disease in the colon was probably found.

One thing I might mention is that with or without stricture it is difficult to detect the development and presence of neoplasm in the colon of these patients. In the series of cases here in this hospital, and probably quite generally for that matter, when cancer has developed in the face of chronic ulcerative colitis, no matter whether it was discovered accidentally or in routine search for it the prognosis has been bad. I think that in this hospital only one patient survived who developed cancer in the face of ulcerative colitis. By the time we know cancer is present, it is too late in most cases.

What can we do to prevent such things from happening? With the improvement in surgical methods and in the pre- and postoperative care, one can now resect a colon much more easily and with much less mortality than twenty years ago; hence we have to consider carefully the advisability of removing the colons of these patients. I am sure that is particularly true in the type of disease that starts in childhood and continues for twenty years before it is first recognized. I think the incidence of cancer is going to be much greater in such a case than in an acute ulcerative colitis of a few weeks' or a few months' duration. In addition to careful sigmoidoscopy, an x-ray examination should be done every six months as long as the colon remains. One other method that may be of some value, especially with the advent of better cytologic technic, is the cytologic study of rectal discharges. That may give us some clue, but I am afraid that by the time cancer cells are recognized it may be too late to save the patient's life.

DR. ARTHUR S. PIER, JR.: Could this be an exacerbation of the ulcerative colitis without cancer?

DR. ELLIS: It could be, without any question. The point in the history of change in the nature of rectal discharge is very important and, I think, indicative of something other than flare-up of his disease.

DR. EDWARD D. CHURCHILL: I agree. There is the possibility of its being a rectal abscess, which could give a similar picture.

DR. WHEELOCK: The patient had x-ray films in the fall but did not come into the hospital until winter. He had been unwilling to have the operation in the fall because he had some big business deal that he could not leave.

CLINICAL DIAGNOSIS

Ulcerative colitis.
?Cancer of the colon.

DR. ELLIS'S DIAGNOSES

Chronic ulcerative colitis.
Carcinoma of colon.

ANATOMICAL DIAGNOSES

Chronic ulcerative colitis.
Adenocarcinomas of colon with metastases.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Dr. Wheelock, will you tell us your findings at operation?

DR. WHEELOCK: He had not one but three cancers of the colon, the exact location of which I cannot remember. At least one fell within the position shown in the x-ray film. There were implants over the peritoneum, so this was not a curative operation, although the colon was removed. We had planned to take out the rectum at the same time if all had been otherwise normal, but since he had an incurable cancer the rectum was not removed.

DR. CASTLEMAN: The striking picture here was the activity of the disease still present, characterized by the petechial hemorrhages and the very smooth, thinned-out, atrophic mucosa. One large tumor was in the region of the splenic flexure and was completely annular. Another was located about 5 cm. away in the transverse colon. The mucosa between the two large tumors was similar to that on either side of the tumors — namely, a very atrophic mucosa with petechial hemorrhages. In between the tumors was a small ulcerating lesion that showed the same type of adenocarcinoma that had apparently developed from a metastatic node. We found numerous metastases in the lymphatic channels between the two tumors, so he probably had two independent tumors with an intervening area of metastasis that eroded into the mucosa. The lymphatics everywhere were plugged with tumor, and the attached lymph nodes also contained tumor. In many areas the tumor showed much colloid degeneration.

How many cases like this have we had, Dr. Ellis?

DR. ELLIS: I do not know what our percentage is, although it has increased in recent years. The last time the cases were assembled, the incidence was about 3 per cent; since then there have been more. Bargen and his co-workers[1] report 5.4 per cent; the Cleveland Clinic[2] reported 3.8 per cent; the Lahey Clinic[3] between 2 and 4.4 per cent.

DR. CASTLEMAN: The Mayo Clinic was the first institution to mention a higher incidence of carcinoma with ulcerative colitis, years and years ago; Dr. Bargen emphasized it, but no one wanted to believe it. Certainly we see it often in young persons; we have had carcinoma associated with ulcerative colitis in a girl of 17.

DR. ELLIS: We had a patient on the Children's Service 18 months ago[4] who was 12 years old, and I know of one other recent patient in the hospital.

DR. CASTLEMAN: Would you go so far as to say that any patient who has severe ulcerative colitis before the age of 20 should have a total removal of the colon?

DR. ELLIS: I think we shall come to that decision. We tend to believe it more and more strongly as we see more of these patients who develop cancer. Furthermore we are now able to resect the colon with greater ease and fewer complications. After ileostomy about 50 per cent of the patients will have to have colon resection because of exacerbations of colitis.

DR. EDGAR A. TAFT: What is the mortality now from resection of the colon?

DR. CHURCHILL: We never have had a very representative figure in the group of patients with ulcerative colitis, because in this group we have included some patients with virulent and active forms of disease, as well as those who have done as well as this man, in whom the mortality rate of removing the colon should be less than 3 per cent.

DR. CASTLEMAN: The usual explanation for the development of carcinoma in ulcerative colitis is by way of a polypoid lesion; that is, a change from the pseudopolyp to a true adenomatous polyp and then to adenocarcinoma. That is probably only one way in which a cancer of the colon develops. There is evidence now to suggest that atrophy of the mucosa is more of a stimulus to the formation of carcinoma than is hyperplasia. We see it, for example, in the stomach in pernicious anemia in which there is atrophy of the mucosa and in which the incidence of carcinoma of the stomach is high. Perhaps the same thing is true in the colon. Certainly the patients who do develop carcinoma with ulcerative colitis are the patients who have had long-standing disease — the average duration is 17 years — and in many of these patients there are no pseudopolyps; by the time carcinoma occurs, the pseudopolyps have disappeared and there is an atrophic mucosa.

REFERENCES

1. Sloan, W. P., Jr., Bargen, J. A., and Gage, R. P. Life histories of patients with chronic ulcerative colitis. *Gastroenterology* **16**:25-38, 1950.
2. Gleckler, W. J., and Brown, C. H. Carcinoma of colon complicating chronic ulcerative colitis. *Gastroenterology* **14**:455-464, 1950.
3. Kiefer, E. D., Eytinge, E. J., and Johnson, A. C. Malignant degeneration in chronic ulcerative colitis. *Gastroenterology* **19**:51-57, 1951.
4. Case Records of Massachusetts General Hospital (Case 36501). *New Eng. J. Med.* **243**:967-970, 1950.

CASE 38172

PRESENTATION OF CASE

A twenty-seven-year-old single woman was admitted to the hospital because of obesity and progressive hirsutism.

Since the age of seven she had been overweight; her maximum weight, fifteen months prior to entry, was 230 pounds; by diet, however, she was able to reduce and maintain her weight at approximately 180 pounds. Excessive hair growth, first observed at the age of sixteen, increased markedly in the few years prior to entry; since then, the patient had plucked her facial hair and shaved her upper chest every two or three days. There was no deepening of the voice. The patient enjoyed male company but avoided it because of embarrassment concerning her hirsutism and obesity. Catamenia began at the age of eleven; until the year prior to entry the menses had been grossly irregular at intervals of 3 to 10 weeks with a heavy flow for five days; then they became more nearly regular. The periods were unaccompanied by cramps. The patient was known to have had hypertension at the age of twelve; since then the systolic blood pressure had ranged between 150 and 200.

The family history revealed parental obesity; the father weighed over 200 pounds (height, 65 inches); the mother had weighed 190 pounds (height, 61 inches) but reduced to 150 pounds following dietary and insulin therapy for severe diabetes.

The past history was essentially unremarkable.

Physical examination revealed a heavy-set young woman, measuring 64 inches in height and weighing 185 pounds. The obesity was generalized. The skin was coarse and oily. There was marked hirsutism of the face, chest, arms, abdomen and, to a lesser extent, the legs. There was no temporal recession of hair. There was +++ acne over the chin and shoulders. Prominent striae were present in the skin of the lower abdomen. The thyroid cartilage was not enlarged, and the voice was of the normal female type. No masses were palpable in the abdomen or flanks. The clitoris was not enlarged. Pelvic examination disclosed a small uterus; no masses or ovaries were palpable in the vaults. The blood pressure was 140 systolic, 95 diastolic.

A catheter specimen of urine, of specific gravity 1.032, was normal. Examination of the blood revealed a hemoglobin of 14.4 gm. and a white-cell count of 8000, with a normal differential. A fasting eosinophil count was 147 per cu. mm. The blood cholesterol was 245 mg. and the fasting blood sugar 104 mg. per 100 cc. The urinary 17-ketosteroid excretion levels were 30.0 and 27.0 mg. per 24 hours on two examinations; 17-ketosteroid levels fourteen and twelve months prior to entry had been 18.8 mg. and 18.9 mg. per twenty-four hours respectively. Combined bilateral perirenal air and pyelographic studies showed minimal disparity in size of the adrenal glands, the left being questionably larger; both glands were of normal contour, however. On the eleventh hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JOE V. MEIGS*: I do not mind saying before I start discussing this case that I am confused. I have no way, from my own experience or from reading the literature, to be sure of the diagnosis.

*Chief, Gynecologic Service, Massachusetts General Hospital.

I should like to see the x-ray films.

DR. JOSEPH HANELIN: The perirenal injection was done first on the left side and a day later on the right side. There is fairly good demonstration of the renal and adrenal areas. In the region of the left adrenal gland is a triangular density that has the appearance of a normal-contoured gland, although it is slightly larger than the right adrenal shadow. The status of the pelvis is shown in a film made about a year before entry, — part of a pyelogram showing the bladder full of dye, — in which no definite masses are visible.

DR. MEIGS: Have you any x-ray films of the bones?

DR. HANELIN: In the films we have there is no osteoporosis.

DR. MEIGS: Have you a picture of the patient showing the distribution of the fat? Was it of the type one sees in Cushing's syndrome or was she just a big husky girl?

DR. ROBERT E. SCULLY: The only statement in the record referable to the distribution of the fat is that it was generalized.

DR. MEIGS: Did this woman have Cushing's syndrome or was she just virilized? There are many points against the diagnosis of Cushing's syndrome. There was no evidence of osteoporosis on the films we have seen. The combination of obese trunk and thin arms and legs characteristic of Cushing's was not present. The skin was coarse and not thin. There was no diabetes. There was no polycythemia — at least one hemoglobin determination was within normal limits. There were abdominal striae, but these may appear in anyone who experiences a rapid stretching of the abdominal wall, as, for example, in pregnancy.

The diagnosis, then, reduces itself to a consideration of all the conditions, adrenal and ovarian, in which virilization occurs.

Did the patient have an adrenal lesion? The minimal x-ray changes are not suggestive of it, but neither do they rule out hyperplasia or even tumor. As far as the adrenogenital syndrome due to adrenal hyperplasia in the fetus is concerned, I rather believe it can be ruled out. Girls with this lesion are of the young Hercules type, have an enlarged clitoris and a deep voice and never develop menses. Adrenal hyperplasia with its onset later in life, however, must be seriously considered. Virilizing tumors of the adrenal gland, — cortical adenomas and carcinomas, — may produce clinical pictures similar to that of the present case. Kinsell and Lisser[1] recently reported an adrenal tumor of which the only symptom was marked hirsutism. There was no deepening of the voice, no enlargement of the clitoris and no amenorrhea. The ketosteroids were high — in the neighborhood of 80 mg. I doubt, however, that our patient had an adrenal tumor, because with these tumors the 17-ketosteroids are usually, though not invariably, higher than hers.

The lesions in the ovaries that can produce virilism include both tumors and various non-neoplastic lesions. The tumors are arrhenoblastomas, lipoid-cell or adrenal rest tumors and hilus-cell tumors. I doubt that I am dealing with an arrhenoblastoma here, because the periods were relatively normal, the voice did not deepen and the clitoris did not enlarge. The non-neoplastic lesions include the Stein–Leventhal syndrome and hilus or Leydig-cell hyperplasia. The Stein–Leventhal syndrome characterized by polycystic ovaries must be considered in patients who are obese and hirsute. This girl, of course, also had hypertension, with its onset before puberty; hypertension is not a part of the Stein–Leventhal syndrome and may be an independent phenomenon in this case. Although the Stein–Leventhal syndrome is often associated with a moderate amount of hirsutism, I think this girl had more than usual, so she may have had a hyperplasia of the hilus cells. These cells, found in the hilus of the ovary, are probably the same as the Leydig cells of the testis.

When one adds up all the signs and symptoms they do not seem to point definitely to any one condition. I am going to have to guess that she had some sort of ovarian disease, probably of the type one sees in the Stein–Leventhal syndrome; the ovaries must have contained, in addition, some sort of cells that were virilizing, possibly hilus or Leydig cells.

CLINICAL DIAGNOSIS

?Ovarian tumor.

DR. MEIGS' DIAGNOSIS

?Stein–Leventhal syndrome, with hilus or Leydig cell hyperplasia of ovaries.

ANATOMICAL DIAGNOSES

Ovarian hyperthecosis.
Reticular zone hyperplasia of adrenals.
(Hirsutism.)

PATHOLOGICAL DISCUSSION

DR. SCULLY: The operation, performed by Dr. Somers H. Sturgis, was an exploration of the ovaries. These were of normal size; sectioning down to the hilus on each side revealed several small cysts beneath the capsule. The striking abnormality, however, was replacement of the central portion by dense stroma. Bilateral wedge resection was done. Microscopically, the ovaries showed hyperplasia of the cortical stroma; disseminated throughout the hyperplastic stroma were multiple foci of large lipoid-laden cells that resembled theca-interna cells (Fig. 1). Likewise, surrounding several cystic and atretic follicles were thick mantles of theca cells. This type of ovarian histology has been described a number of times in virilized women and has been designated as "diffuse luteinization"[2] or "hyper-

thecosis"[3] of the ovaries. Histologically it overlaps the Stein–Leventhal syndrome, and, indeed, transitional forms between the two syndromes occur clinically. A third similarity to the Stein–Leventhal syndrome is the occasional symptomatic improvement following wedge resection of the ovaries.

At the time we examined these ovaries, several years ago, we were not satisfied that the pathologic

FIGURE 1. *Photomicrograph of Ovary.*
Note central nest of large clear cells in ovarian stroma. At top center are four ova.

changes therein sufficed to explain this woman's hirsutism and elevated 17-ketosteroids; consequently, about four weeks after the first operation, Dr. Oliver Cope explored the left adrenal. The gland was grossly unremarkable and was of normal size; one third of it was resected. Microscopically, the innermost layer of cells, which stained deeply eosinophilic and had the appearance of zona reticularis, was quite broad, occupying from 50 to 60 per cent of the thickness of the entire cortex (Fig. 2). In the usual adrenal, this eosinophilic zone is about one third or at most one half this broad. This type of histologic picture, so-called hyperplasia of the reticular zone of the adrenal, has been described by a number of investigators as the pathologic background for the adrenogenital syndrome.[4, 5]

In summary, then, we seem to have combined in this case the histologic findings that are seen in ovarian virilism and in the so-called adrenogenital syndrome. I think that if we had examined only the ovaries we might have pigeonholed this woman as a case of ovarian virilism, whereas if we had studied only the adrenal we might have called this a typical case of the adrenogenital syndrome. In view of the fact that only a negligible number of cases of virilism have been studied pathologically from both adrenal and ovarian aspects, one may well question whether the distinction among the adrenogenital syndrome, ovarian hyperthecosis and the closely related Stein–Leventhal syndrome is not an unscientific one, based on incomplete pathological study. This particular case, although it may be the exception rather than the rule, suggests that virilism may be a pluriglandular disorder and that actually these three syndromes may be, if not in certain cases identical, at least variants of the same

FIGURE 2. *Photomicrograph of Adrenal Gland.*
Note central deeply staining zone in contrast to peripheral clear zone.

disorder. This point of view has recently been suggested in a monograph by Du Toit.[6]

DR. FULLER ALBRIGHT: I wonder whether both theca luteinization and the hyperplasia of the reticular zone are not secondary to overfunction of some pituitary hormone — luteinizing hormone? luteotrophin? or both?

DR. SCULLY: The histologic changes certainly suggest that something was going on in the pituitary to stimulate both adrenal and ovary. Experimental evidence has been adduced that both the theca cells and the cells of the reticular zone may be androgenic,[5, 7] so it is conceivable that they respond to the same pituitary hormone.

DR. JACOB LERMAN: Have you examined the adrenals of patients with the Stein–Leventhal syndrome?

DR. SCULLY: No, we have not.

DR. LERMAN: Theoretically they should be stimulated and hyperplastic.

DR. SCULLY: Theoretically they may be; I think many suspect that the adrenals are involved in the Stein–Leventhal syndrome. In a number of Broster's cases[8] of so-called adrenogenital syndrome, the ovaries were described as being cystic at the time of operation.

DR. MEIGS: I think Du Toit, in his monograph,[6] says that some of the patients who have been operated on for virilism and who have shown lesions of the adrenal have had abnormalities of the ovaries similar to the Stein–Leventhal syndrome, whereas others have not.

DR. SCULLY: In most of the cases in which adrenal exploration was done, the ovaries were only examined grossly, or if they were examined microscopically they were not described in any detail.

DR. MEIGS: Microscopically, did you have a chance to examine the hilus of the ovary in this case? She may have had some hilus-cell hyperplasia.

DR. SCULLY: No; we do not know what the hilus cells are doing in any of these syndromes, because the resected portions of ovaries almost never include hilus.

DR. MEIGS: In other words, when one is operating on these patients with a question of ovarian disease, it seems to me that it is very important to make available to the pathologist, if possible, a biopsy of the hilus.

DR. HANELIN: Has there been any change in the patient postoperatively?

DR. SCULLY: The 17-ketosteroid determinations done five months after the second operation were within normal range and remained there.

DR. ALBRIGHT: She has remained essentially unchanged clinically.

REFERENCES

1. Kinsell, L. W., and Lisser, H. Adrenal cortical tumor causing hirsutism without other evidence of virilization. *J. Clin. Endocrinol.* **12**: 50-54, 1952.
2. Geist, S. H., and Gaines, J. A. Diffuse luteinization of ovaries associated with masculinization syndrome. *Am. J. Obst. & Gynec.* **43**: 975-983, 1942.
3. Fraenkel, L. Thecoma and hyperthecosis of ovary. *J. Clin. Endocrinol.* **3**:557-559, 1943.
4. Goldzieher, M. A., and Koster, H. Adrenal cortical hyperfunction. *Am. J. Surg.* **27**:93-106, 1935.
5. Blackman, S. S., Jr. Concerning function and origin of reticular zone of adrenal cortex: hyperplasia in adrenogenital syndrome. *Bull. Johns Hopkins Hosp.* **78**:180-217, 1946.
6. Du Toit, D. A. H. *Polycystic Ovaries, Menstrual Disturbances and Hirsutism. Hyperthecosis.* 161 pp. Leiden: H. E. Stenfert Kroese, N. V., 1951.
7. Parkes, A. S. Androgenic activity of ovary. In *Recent Progress in Hormone Research.* Vol. 5. 537 pp. New York: Academic Press, 1950. Pp. 101-109.
8. Broster, L. R. Eight years' experience with adrenal gland. *Arch. Surg.* **34**:761-791, 1937.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

THE RED CROSS BLOOD PROGRAM AND THE PHYSICIAN

ON February 25, 1952, E. Roland Harriman, president of the American National Red Cross, issued a report on the National Blood Program to the chapter chairmen. The report in its general tone is optimistic on the basis of past accomplishments. Some of its highlights are worth reprinting.

At present the Red Cross is operating 44 regional blood programs, which incorporate a part of a state, a whole state or parts of several states and provide blood for local hospitals as well as for defense. It also operates 15 defense blood programs, which provide blood and plasma for the Armed Forces. Cooperating in defense blood collection are some 33 private blood banks. In the seven months from July 1, 1951, to February 1, 1952, these three programs collected 1,195,211 pints of blood for defense. In addition, the Red Cross provided 902,622 pints for civilian hospitals. This is an achievement for which the Red Cross and the co-operating banks should be congratulated. It is, however, but a beginning. More whole blood will be needed for Korea. Much more plasma must be stockpiled for the Armed Forces and civil defense, and the civilian-hospital needs are both large and continuous. To meet these needs the effort must be continuous.

Two important factors are responsible for the success of the Red Cross. The first is money; the second is donor recruitment. Some of the money is supplied by the government, but all that supports the collection of blood for our own hospitals is raised by private subscription. Any help that can be given the Red Cross in raising funds will have a direct effect on the transfusion therapy of patients in these hospitals.

Donor recruitment is largely dependent on good publicity. The Defense Department is providing this over the radio, by television and in various other ways. In order to secure donors, however, personal contact and door-to-door recruitment are vital. In making recruitment effective the physician has an important role to play. He can contact the relatives of patients who have received blood and tell them that it must be replaced. He can explain to his patients the benefits derived from the blood program. He can help his local Red Cross Chapter with its problems and further better relations with the hospital blood bank. He can speak at meetings about the necessity of transfusion in patient care. Lastly, he can give blood himself and set an example in his community.

All who have seen the benefits to patients from this program and who realize the necessity of whole blood and plasma for the Armed Forces and the dire need of plasma for civil defense realize that a continued effort must be made to bring in blood. In a large sense this is the blood program of the practicing profession, and it is up to the profession to make it work.

HARVARD NECROLOGY

THE annual report of the President of Harvard University, recently distributed, contains a section on the losses by death that the University has sustained in the past year. Eight of those listed are

from the ranks of medicine; seven, as fellows of the Massachusetts Medical Society, have already received more or less mention in these columns. The President's report provides the occasion to record a final valediction on this group as a whole, each member of which had served his university and his profession so well.

Four of these physicians, their service finished, had reached the retired list; their ages aggregated three hundred and thirty-five years. Alfred Worcester, the dean of practitioners, Henry K. Oliver Professor of Hygiene, emeritus, died in August in his ninety-seventh year; Henry Asbury Christian, Hersey Professor of the Theory and Practice of Physic, emeritus, died also in August, in his seventy-sixth year; Frederick Thomas Lewis, James Stillman Professor of Comparative Anatomy, emeritus, — not a fellow of the Massachusetts Medical Society, — died in June in his seventy-seventh year, and Walter Brackett Lancaster, lecturer on ophthalmology, retired, died in December in his eighty-ninth year. Like old warriors, their battles over, they went to their accounting.

More tragic is the loss of four members of the University's faculty who died while still on active duty. Tracy Burr Mallory, professor of pathology at the Massachusetts General Hospital, died in November in his fifty-sixth year; William Lloyd Aycock, associate professor of preventive medicine and hygiene, died in October in his sixty-third year; George Marshall Crawford, instructor in dermatology and onetime acting head of the department, died in October in his forty-sixth year, and Autino Fiore, instructor in public health and Health Commissioner of the city of Cambridge, — the youngest health commissioner in the state, — died in October in his thirty-fifth year.

The scales are too evenly balanced: four died full of years and four still full of promise, whether at thirty-four years of age or sixty-two.

THE ISAAC RAY MEDICAL LIBRARY AT THE BUTLER HOSPITAL

In March, 1952, there was dedicated at the Butler Hospital in Providence a medical library named after Isaac Ray, one of the founders of the American Psychiatric Association (in 1844) and superintendent of the Butler Hospital from 1846 to 1867. It is fitting that this psychiatric library should carry the name of a distinguished American psychiatrist who was expert in his day in the treatment of mental disease and was also an authority on medicolegal matters connected with psychiatry. He wrote many books and articles, the one best known to the current generation being "A Treatise on the Medical Jurisprudence in Insanity."

It is planned to build up the library to about 10,000 volumes on psychiatry and closely related subjects. About one fifth of the books are already at hand. The librarian, moreover, has embarked on an important bibliographic project that will have great importance in relation to education and research in this country. A union catalogue of all psychiatric material in the United States is to be established similar to the Union Catalogue of the Library of Congress for general literature. Such a catalogue would contain information about the location of all important books on psychiatry in this country.

At the dedication ceremony on March 5, 1952, Dr. Leo H. Bartemeier, president of the American Psychiatric Association, brought official greetings, and the general purpose of the Library was explained by Dr. Gregory Zilboorg, consultant in psychotherapy and research to the Butler Hospital. The Aquinas Fund, of which Dr. Zilboorg is a trustee, provided funds for the purchasing of books as well as financial compensation for the medical librarian.

The Isaac Ray Medical Library, so well organized and fittingly named, will be welcomed by the medical profession of the United States and will soon take its place among the national libraries in America. The union catalogue, unique in character, when widely known should be of aid to librarians and psychiatrists doing research in the psychiatric field.

EX FENESTRA

An event in history, dimly recalled, pertains to the classical solution of a political problem in which certain Bohemian councilors were ejected from a castle window, thus inaugurating the Thirty Years' War. Windows have undoubtedly been used before as well as since that time on similar occasions, but history has dignified this episode with the title "*Ex Fenestra.*"

A well known life insurance company, mindful of the fact that spring is here and doubtless remembering this historic event, has warned the world at large that *ex fenestra* is a perennial hazard — that windows in fact have a habit of being fallen out of, and that more persons are likely to fall out of them when they are open than when they are closed. This observation emphasizes the seasonal factor, to be borne in mind as the time for open windows draws near, when storm windows are removed, rugs are shaken and screens are installed, each of which operations occasionally introduces the problem of the aftercoming householder.

Falls from windows, according to this source of information, are responsible for about 500 deaths annually in the United States, with the nonfatal accidents unrecorded. Eighty per cent of the fatal falls occur in — or from — the home; they are most frequent in those otherwise salubrious seasons when, as the report reiterates, windows are most likely to be open.

A lady, belonging to Bangor, Me., assures us that a neighbor of hers has three well-developed mammae — and further, that while rearing her children, they were nursed, indifferently, on all three.

Boston M. & S. J., *April 28, 1852*

MASSACHUSETTS MEDICAL SOCIETY

TO THE LADIES

The members of the Woman's Auxiliary to the Massachusetts Medical Society, speaking for the wives who are not Auxiliary members as well as for themselves, urge their husbands to bring home that part of the literature concerning the Annual Meeting that pertains to the activities of the ladies.

This is enclosed with the material that is being sent to all fellows of the Society.

DEATHS

BACHMANN — Rudolph F. Bachmann, M.D., of Fitchburg, died on November 12, 1951. He was in his forty-fifth year.

Dr. Bachmann received his degree from Cornell University Medical College in 1932. He was a former president of the Worcester North District Medical Society, a member of the American College of Surgeons, the New England Obstetrical and Gynecological Society and the Massachusetts Medico-Legal Society and a fellow of the American Medical Association.

He is survived by three children.

SMITHWICK — Marsena P. Smithwick, M.D., of Marblehead, died on March 30. He was in his eighty-fifth year.

Dr. Smithwick received his degree from Harvard Medical School in 1895. He was a fellow of the American Medical Association.

He is survived by his widow and two children.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The May schedule for Consultation Clinics for Crippled Children in Massachusetts follows:

Orthopedic Clinics	Date	Clinic Consultant
Greenfield	May 1	Charles L. Sturdevant
Lowell	May 2	Albert H. Brewster
Salem	May 5	Paul W. Hugenberger
Haverhill	May 7	William T. Green
Brockton	May 8	George W. Van Gorder
Lynn*	May 12	Daniel M. Killoran; John J. Crowley
Gardner	May 13	Carter R. Rowe
Worcester	May 16	John W. O'Meara
Springfield	May 20	Garry deN. Hough, Jr.
Pittsfield	May 21	Edward J. Coughlin, Jr.
Hyannis	May 22	Paul L. Norton
Fall River	May 26	David S. Grice

Rheumatic-Fever Clinics	Dates
North Reading	May 6, 13, 20, 27
Fitchburg	May 7, 14, 21, 28

Plastic Clinics	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon
Western Massachusetts	Monthly	Joseph M. Baker

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

REGULATIONS FOR PHYSICAL EXAMINATION OF SCHOOL CHILDREN IN MASSACHUSETTS

The Department of Public Health, acting under the authority of Section 57, Chapter 71 of the General Laws, Tercentenary Edition, as amended by Chapter 502 of the Acts of 1951 hereby prescribes and establishes the following rules and regulations relative to the physical examination of school children.

These regulations become effective September 1, 1952, as provided in Chapter 502, Acts of 1951.

Regulations for Medical Examination of School Children in Massachusetts

Preamble

The purpose of these regulations is to discover disabilities of school children as soon as possible so as to enable all children to obtain the fullest benefit of their educational opportunities and to insure that diseases dangerous to the public health and other contagious or communicable diseases are recognized whenever they occur.

The school health program should encourage the performance of the health appraisal by the family's own physician whenever possible. The results of the family physician's examination shall be recorded on health record forms supplied by the State Department of Public Health through the schools or on such health record forms as are supplied by the schools, after approval by the Department of Public Health. A copy of this record containing the results of the examination and the physician's recommendations shall be returned to the school. The family physician performing the health appraisal of a school child shall be furnished with a copy of the records of screening tests performed in the school.

The school committee or the board of health shall provide the services of a school physician to carry out health appraisals on such children as do not have this service performed by the family physician. He shall carry on other responsibilities of the school health program including (1) interpretation of the child's health situation to the school personnel, (2) assistance to the teacher and nurse in meeting the health needs of the child insofar as this is possible in the school environment, and (3) interpretation of the school health program to the family physician and parent. The services of the school physician shall be co-ordinated in the total school health program. He shall be responsible for the control of communicable disease and give assistance in the formulation of the health education program.

Regulations

1. The school committee or board of health shall cause every child in the public schools to be separately and carefully examined by a physician duly registered in Massachusetts within six months before entrance to school or during the first year after entrance and at intervals of either three or four years thereafter. A child transferred from another school system shall be examined as an entering child unless school health records are transferred with the child showing that he has had an adequate health appraisal in the school year of transfer.

2. The school committee or the board of health shall cause children in the public schools to be separately and carefully examined by a duly registered physician under the following circumstances.

2.1 Children returning after an absence from school of five consecutive school days or more due to illness.

2.2 Children referred because of frequent absences due to unexplained illnesses.

2.3 Children referred because of known physical defects that require repeated appraisal.

2.4 Children referred from teacher-nurse conferences because the child is not making expected progress in school or because of signs of illness noted by the teacher or nurse.

2.5 Children under 16 and over 14 years of age requesting employment certificates.

2.6 Children planning to participate in competitive athletics annually, previous to such participation.

3. The school committee or board of health shall regularly make provision that each child may meet with the school physician in conference, with or without the presence of a third person at the discretion of the physician.

4. The school committee or board of health shall cause the vision and hearing of each child in the public schools to be tested in the first grade and every second year thereafter.

4.1 The hearing of each child shall be tested by means of some form of discrete frequency hearing test such as the Massachusetts Hearing Test.

4.2 The vision of each child shall be tested by means of the Massachusetts Vision Test.

4.3 Tests of sight and hearing shall be performed by teachers, physicians, optometrists, nurses or others who are approved by the Massachusetts Department of Public Health for this purpose and in accordance with instructions set up by the Department. (Such personnel may request necessary training from the Massachusetts Department of Public Health. The Department's instructions regarding vision and hearing testing may be procured from the Division of Maternal and Child Health, 88 Broad Street, Boston.)

5. The school committee or board of health shall cause each child's weight and height to be measured annually.

6. The health appraisal shall be done with such care and detail as to command medical respect and be a desirable educational experience for the child. Rectal and vaginal examinations shall not be done by the school physician.

6.1 All appraisals shall be done in the presence of a third person and in a reasonable degree of privacy. The child shall be undressed sufficiently to permit an adequate appraisal.

6.2 Sufficient time shall be allotted for an adequate appraisal of each child.

6.3 The appraisal shall include time for a conference with the parent or child concerning the child's growth and development and the findings of the health appraisal.

6.4 The school authorities shall invite the parent or parents of the entering child and of the child in the fourth grade to be present during the appraisal by the physician.

7. Disabilities and defects found on health appraisal of an individual child shall be brought to the attention of the family. The school or health department shall encourage the family to take the child with physical defects to the family physician or other source of care.

8. The school physician shall examine at any time, including the required intervals, and previous to participation in competitive athletics, each child to determine the presence or absence of diseases dangerous to the public health and other communicable or contagious diseases, in consonance with the last line of Section 57 of Chapter 71 of the General Laws as most recently amended by Chapter 502 of the Acts of 1951.

9. The above are minimum regulations for the examination of school children in Massachusetts. The school committee or board of health may provide for more frequent and more specialized examinations or both if it wishes to do so.

10. Results of these health appraisals shall be recorded in detail on health record forms provided by or approved by the Massachusetts Department of Public Health.

BOOK REVIEWS

Emotions and Clinical Medicine. By Stanley Cobb, M.D., Bullard Professor of Neuropathology, Harvard Medical School, and psychiatrist-in-chief, Massachusetts General Hospital. With an introduction on semantics and definitions by John R. Reid, Ph.D. 8°, cloth, 243 pp., with 19 illustrations. New York: W. W. Norton and Company, Incorporated, 1950. $3.00.

Emotions and Clinical Medicine is a lucid discussion of a subject that is all too frequently obscured by poorly defined thinking and discussion. The general tone of this volume is indicated by the introduction on semantics and definitions. All who think and work in the field of emotions and human behavior recognize the need of specifically defined terminology; this thought is emphasized in the book. There is presented a well rounded discussion of the cortex in its relation to emotionality and its secondary physiologic changes. A compilation and re-emphasis of a great deal of experimental and clinical work associated with the hypothalamus is presented to clarify some obscure points and to indicate the need of further investigation. Chapters concerning clinical problems and social significance are clear cut and of decided interest.

In general, this work re-emphasizes the anatomicophysiologic relation between emotionality and abstract ideas and points the way to a more profound and broad way of thinking.

HUBERT A. CARBONE, M.D.

Ugo Benzi: Medieval philosopher and physician, 1376–1439. By Dean P. Lockwood. 8°, cloth, 441 pp. Chicago: University of Chicago Press, 1951. $8.00.

Professor Lockwood has written a comprehensive critical study of the life and period of Ugo Benzi, contemporarily known as Hugo Senensis. Many of the details of his life are taken from the *Vita Ugonis*, a manuscript biography written about 1440 by his son, Socino Benzi. This manuscript is preserved in the Biblioteca Communal at Ferrara (Antonelli 545) and forms part of a miscellany of literary opuscula and theological documents associated with the Ferrara-Florence Church Council. The manuscript is the first item in the volume; according to Lockwood, it is a "unique addition to our understanding of the period."

Hugo was the author of a number of medical works on medical theory, — the "five great commentaries," — and on practical medicine — the *consilia* and the separate treatises.

The text proper is devoted to the biography, an analysis of the works and an interesting account of medicine and physicians of the fifteenth century.

The appendixes supporting the text present a chronologic outline of Hugo's life, extracts from his works, especially from the *consilia*, the formation of the corpus (*consilia* and treatises) and a list of the manuscripts and printed editions, with a census of the existing copies and their locations. The unique biography of Hugo by his son is probably the first historical biography of a physician; a full translation is given in Chapter 2. To the text are appended special indexes to the *consilia*, and there is a good general index. The publishing is excellent and the price is reasonable. This scholarly, comprehensive work should be in all historical collections, general and medical.

JAMES F. BALLARD

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Letters of Benjamin Rush. Edited by L. H. Butterfield. In 2 volumes. 8° cloth. Volume 1: 1761-1792, 624 pp. Volume II, 1793-1813, 670 pp. Princeton, New Jersey: Princeton University Press, 1951. $15.00 the set.

Dr. Rush was one of the most distinguished American physicians of the eighteenth century, with many interests other than his profession, including politics, social life and chemistry. He was a prolific letter writer and corresponded with the first five Presidents of the United States and with leading American and European scientists. The two volumes of his letters contain over 650, two thirds of them never before printed. Two major series have to do with the failure of the Continental hospital service in the Revolution and the Philadelphia yellow-fever epidemic of 1793. The printing is good, with a clear type face and a substantial non-glare paper; the publishing is excellent. The set should be in all collections on medical history and, naturally, in all collections of Americana.

Instruments and Apparatus in Orthopaedic Surgery. By E. J. Nangle, M.B., Ch. B., F.R.C.S. 8°, cloth, 231 pp., with 200 illustrations. With a preface by H. J. Seddon and Joseph Trueta, M.D. Springfield, Illinois: Charles C Thomas, 1951. $9.50.

Mr. Nangle presents a selection of apparatus used in various orthopedic conditions. Designs and manufacturers of the various appliances are discussed in detail, with extensive illustration. Special attention is given to plaster and the various plastics. There are author and subject indexes and the book is well published. It is recommended for all collections on the subject.

Incontinence in Old People. By John C. Brocklehurst, M.D., Major, R.A.M.C. With a foreword by Stanley Alstead, M.D., F.R.C.P., Regius Professor of Materia Medica and Therapeutics, University of Glasgow. 8°, cloth, 191 pp., with 62 illustrations. Edinburgh: E. and S. Livingstone, Limited, 1951. $6.50.

This special monograph is divided into three major parts. The first consists of a review of the previous literature on urinary and fecal incontinence. Parts II and III discuss etiology and treatment in old age. The publishing is excellent, and the volume should be in collections on urology and gastroenterology.

Dible and Davie's Pathology: An introduction to medicine and surgery. By J. Henry Dible, M.B. (Glas.), F.R.C.P. (Lond.), professor of pathology, University of London (Post-Graduate Medical School of London). Third edition. 8°, cloth, 963 pp., with 417 illustrations, including 9 plates in color. Philadelphia: J. B. Lippincott Company, 1950. $13.00.

This third edition of a standard textbook has been thoroughly revised; much of the contents has been rewritten, and large sections have been extensively altered to bring the material up to date. The book has been written primarily for the medical student. The printing is well done and the illustrations are excellent. There is an extensive index of 42 pages.

The Health of the Mind. By J. R. Rees, M.D., director, World Federation for Mental Health. 8°, cloth, 207 pp., with 4 illustrations. New York: W. W. Norton and Company, Incorporated, 1951. $2.75.

In this book for the layman Dr. Rees discusses the problems of mental health from early life through childhood and adolescence to maturity. There is a special chapter on sex education. The text is written in simple, understandable English, and the book should prove valuable as a condensation of the subject. There is a good index, and the printing is well done.

The Architecture of Normal and Malformed Hearts: A phylogenetic theory of their development. By Alexander Spitzer, M.D. With a summary and analysis of the theory by Maurice Lev, M.D., associate professor of pathology, University of Illinois College of Medicine, and associate pathologist, University of Illinois Hospitals, Chicago, and Aloysius Vass, M.D. With a foreword by Otto Saphir, M.D., pathologist, Michael Reese Hospital, and clinical professor of pathology, University of Illinois College of Medicine, Chicago. 8°, cloth, 145 pp., with 30 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $5.00.

This English translation of Spitzer's phylogenetic theory of the septation process in the normal heart and of cardiac malformation is of outstanding importance. The book should be in all collections on cardiology.

Leitfaden der Laparoskopie und Gastroskopie. By Prof. Dr. Med. H. Falk, Leitender Arzt der inneren Abteilung des Stadtkrankenhauses Kassel, and W. Brühl, Dr. Med. Habil, Chefarzt der Inneren Abteilung des Paulinenhospitals Arolsen. 8°, cloth, 159 pp., with 82 illustrations, partly in color. Stuttgart: Georg Thieme, 1951. Ganzleinen DM 27. Distributed by Grune and Stratton, Incorporated, New York.

This manual on the visual examination of the abdominal organs by the laparoscope and of the stomach by the gastroscope is well written. Although it is condensed, the two technics are well covered. The publishing is excellent; the illustrations are particularly good. Lists of references are appended to both parts, and there is an author index. The book should be in all collections on these subjects.

NOTICES

ANNOUNCEMENT

Dr. Lyman H. Hoyt announces the opening of an office for the practice of internal medicine at 51 Bay State Road, Boston, in association with Dr. George E. MacDonald.

NEW ENGLAND PEDIATRIC SOCIETY

The spring meeting of the New England Pediatric Society will be held on Friday, May 16, at the Mary Hitchcock Hospital, Hanover, New Hampshire.

Hotel reservations may be made at the Green Lantern, Hanover, or at Norwich Inn, Norwich, Vermont.

CHILDREN'S CANCER RESEARCH FOUNDATION

The Children's Cancer Research Foundation will present two lectures in the auditorium of the Jimmy Fund Building, 35 Binney Street, Boston.

On May 13 at 4:30 p.m. Dr. Kurt G. Stern, adjunct professor of biochemistry at the Polytechnic Institute of Brooklyn, will speak on "Studies on the Interaction of Rare Earth Compounds with Nucleic Acids and Nucleoproteins in Vitro and in Vivo."

On May 20 at 5:00 p.m. Dr. Balduin Lucké, professor of pathology at the University of Pennsylvania School of Medicine, will speak on "The Influence of Environmental Factors on the Growth and Form of Cancer."

NEW YORK SOCIETY FOR CIRCULATORY DISEASES

The New York Society for Circulatory Diseases will hold its fourth regular meeting at 8:30 p.m. on June 5, in the Keystone Room of the Hotel Statler, New York City.

Further information may be obtained from Dr. Gabriel F. Greco, Secretary, the New York Society for Circulatory Diseases, Inc., 114-08 Linden Boulevard, Ozone Park 16, New York.

SOCIETY FOR INVESTIGATIVE DERMATOLOGY, INCORPORATED

The thirteenth annual meeting of the Society for Investigative Dermatology, Inc., will be held at the Hotel Sherman, Chicago, Saturday and Sunday, June 7 and 8.

Further information may be obtained from the Secretary-Treasurer, Dr. Herman Beerman, 255 South 17th Street, Philadelphia 3, Pennsylvania.

SOCIETY MEETINGS AND CONFERENCES

APRIL 25 AND 26. Texas Medical Center. Page 354, issue of February 28.

APRIL 25 AND 29. Boston City Hospital House Officers' Association. Page 459, issue of April 3.

APRIL 26. Boston City Hospital Alumni Association. Page 476, issue of March 20.

APRIL 26. Alumni Association of Long Island College of Medicine. Page 434, issue of March 13.

APRIL 28–30. Postgraduate Lecture Course. Page 633, issue of April 17.

APRIL 29. Children's Medical Center. Page 635, issue of April 17.

APRIL 30. Middlesex West District Medical Society. Hotel Kendall, Framingham. 6:15 p.m.

MAY 1–3. American College Health Association. Page 634, issue of April 17.

MAY 3. New England Society of Anesthesiologists. Page 595, issue of April 10.

MAY 3. Boston University School of Medicine Alumni Association. Page 560, issue of April 3.

MAY 3–31. Springfield Hospital. Page 635, issue of April 17.

MAY 4–9. Society for Pediatric Research and the American Pediatric Society. Hotel Chamberlain, Old Point Comfort, Virginia.

MAY 6–JUNE 3. Boston City Hospital House Officers' Association. Page 634, issue of April 17.

MAY 7. Massachusetts Society of Examining Physicians. Page 595, issue of April 10.

MAY 8. The Choice of Patients for the Surgical Treatment of Hypertension. Dr. James A. Evans. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

MAY 8–10. American Neurological Association. Page 559, issue of April 3.

MAY 10. Boston Dispensary Proctologic Session. Page 433, issue of March 13.

MAY 10 AND 11. American Electroencephalographic Society. Page 390, issue of March 6.

MAY 11–17. Pan-American Convention of Gastroenterology. Page 434, issue of March 13.

MAY 13. Springfield Academy of Medicine. Page 635, issue of April 17.

MAY 13. New England Society of Anesthesiologists. Page 635, issue of April 17.

MAY 13 AND 20. Children's Cancer Research Foundation. Notice above.

MAY 15–17. American College of Surgeons. Page 596, issue of April 10.

MAY 16. New England Pediatric Society. Notice above.

MAY 19–22. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 19–23. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

MAY 21 AND 22. Venereal-Disease Seminar. Page 559, issue of April 3.

MAY 22–24. American Academy of Pediatrics. Page 522, issue of March 27.

MAY 24. Annual Meeting. Massachusetts Association of Medical Technologists, Inc.

MAY 26–28. Minnesota State Medical Association. Annual Meeting. Page 316, issue of February 21.

MAY 26–29. National Tuberculosis Association. Copley Plaza and Statler hotels, Boston.

MAY 29–31. American Academy of Dental Medicine. Page 476, issue of March 20.

JUNE 5. New York Society for Circulatory Diseases. Notice above.

JUNE 5–8. American College of Chest Physicians. Page 280, issue of February 14.

JUNE 7 AND 8. Society for Investigative Dermatology, Inc. Notice above.

JUNE 18–20. Massachusetts Public Health Conference. Amherst.

JUNE 19–21. American Association of Genito-Urinary Surgeons. Page 434, issue of March 13.

JUNE 22–26. American Society of Medical Technologists. Twentieth Annual Convention. Portland, Oregon.

JULY. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.

JULY 7–11. International Congress of Dietetics. Page 434, issue of March 13.

JULY 7–12. International Diabetes Federation. Page 316, issue of February 21.

JULY 8–11. Thirteenth British Congress of Obstetrics and Gynecology. Page 916, issue of December 6.

JULY 14–19. International Congress of Physical Medicine. Page 998, issue of June 28.

JULY 24–26. Conference on Aging. Page 559, issue of April 3.

AUGUST 25–29. American Congress of Physical Medicine. Page 476, issue of March 20.

AUGUST 31–SEPTEMBER 6. Interamerican Congress of Cardiology. Page 422, issue of March 27.

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies. Mount Washington Hotel, Bretton Woods, New Hampshire.

OCTOBER 28–30. New England Postgraduate Assembly. Hotel Statler, Boston.

OCTOBER 29. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

NOVEMBER 3–7 AND 10–21. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

JULY, 1953. International Congress on Medical Librarianship. Page 316, issue of February 21.

DISTRICT MEDICAL SOCIETIES

HAMPSHIRE

MAY 7. Annual Meeting. Jones Library, Amherst.

MIDDLESEX SOUTH

APRIL 30. Hotel Continental, Cambridge.

(*Notices concluded on page xv*)